

[NAME OF DOCUMENT] Specification

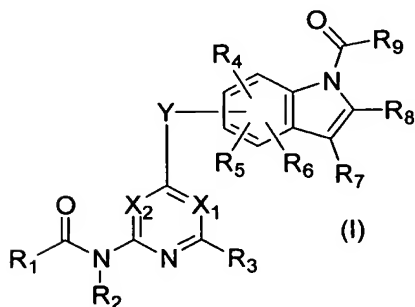
[TITLE OF INVENTION] NITROGEN-CONTAINING AROMATIC DERIVATIVES

[WHAT IS CLAIMED IS]

5 [Claim 1]

A compound (except N1-cyclopropyl-5-((2-((2-chloroethylamino)carbonyl)amino)-4-pyridyl)oxy)-1H-1-indolecarboxamide) represented by the general formula:

10 [chemical formula 1]

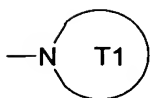


wherein X_1 represents a nitrogen atom or a group represented by the formula $-CR_{10}=$, X_2 represents a nitrogen atom or a group represented by the formula $-CR_{11}=$, and X_1 and X_2 do not represent a nitrogen atom at the same time;

Y represents an oxygen atom, a sulfur atom, a sulfinyl group, a sulfonyl group, or a group represented by the formula $-NR_Y-$ (wherein R_Y represents a hydrogen atom or a C_{1-6} alkyl group);

R_1 represents an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-10} aryloxy group, a group represented by the formula $-NR_{12a}R_{12b}$, or a group represented by the formula

[chemical formula 2]

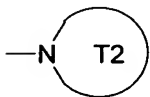


(wherein T1 represents an optionally substituted 5- to 10-membered aromatic heterocycle which may have X in the ring or an optionally substituted 3- to 10- membered heterocycle which may have X in the ring);

R₃, R₄, R₅, R₆, R₇, R₈, R₁₀ and R₁₁ each independently represent a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₈ cycloalkyl group, a group represented by the formula -CO-R₁₃, a group represented by the formula -NR₁₄-CO-R₁₃, a group represented by the formula -SO₂-R₁₅, a group represented by the formula -NR₁₄-SO₂-R₁₅, or a group represented by the formula -NR_{16a}R_{16b};

R₉ represents a group represented by the formula -NR_{16a}R_{16b} or a group represented by the formula

[chemical formula 3]



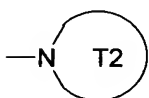
(wherein T2 represents an optionally substituted 5- to 10-membered aromatic heterocycle or an optionally substituted 3- to 10- membered heterocycle);

R_{12a} and R_{12b} each independently represent a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally

substituted C₃₋₆ alkenyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted 3- to 10-membered heterocyclic group, or an optionally substituted C₁₋₆ alkoxy group;

R₁₃ represents a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted 5- to 10-membered heteroaryl group, an optionally substituted 3- to 10-membered heterocyclic group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₆₋₁₀ aryloxy group, a group represented by the formula -NR_{12a}R_{12b}, or a group represented by the formula

[chemical formula 4]



(wherein T2 represents an optionally substituted 5- to 10-membered aromatic heterocycle or an optionally substituted 3- to 10-membered heterocycle);

R₂ and R₁₄ each independently represent a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₈ cycloalkyl group, or a group represented by the formula -CO-R₁₃;

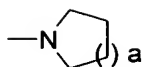
R₁₅ represents an optionally substituted C₁₋₆ alkyl group,

an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted 5- to 10- membered heteroaryl group, or an optionally substituted 3- to 10- membered heterocyclic group;

R_{16a} and R_{16b} each independently represent a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₃₋₆ alkenyl group, an optionally substituted C₃₋₆ alkynyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted 5- to 10- membered heteroaryl group, an optionally substituted 3- to 10- membered heterocyclic group, or an optionally substituted C₁₋₆ alkoxy group; and

X represents an oxygen atom, a sulfur atom, a carbonyl group, a sulfonyl group, a group represented by the formula -CR_{X1}R_{X2}-, or a group represented by the formula -NR_{X3}- (wherein R_{X1}, R_{X2} and R_{X3} each independently represent a hydrogen atom or a group represented by the formula -A₁-A₂-A₃ (wherein A₁ and A₂ each independently represent a single bond, an optionally substituted C₁₋₆ alkylene group or a carbonyl group; and A₃ represents a hydrogen atom, a C₃₋₈ cycloalkyl group, a group represented by the formula -NR_{A1}R_{A2}, or the formula -OR_{A3} (wherein, R_{A1}, R_{A2} and R_{A3} each independently represent a hydrogen atom or a C₁₋₆ alkyl group), or an optionally substituted group represented by the formula

[chemical formula 5]



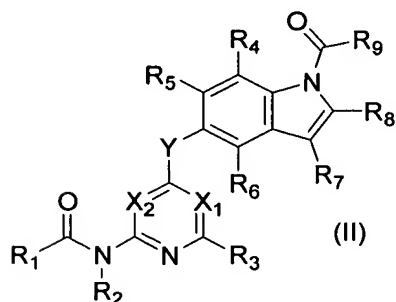
(wherein a represents 1 or 2))),

a salt thereof, or a hydrate of the foregoing.

5 [Claim 2]

A compound (except N1-cyclopropyl-5-((2-((2-chloroethylamino) carbonyl) amino)-4-pyridyl)oxy)-1H-1-indolecarboxamide) represented by the general formula:

10 [chemical formula 6]



wherein X₁, X₂, Y, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ represent the same definitions as X₁, X₂, Y, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ in claim 1, respectively,

15 a salt thereof, or a hydrate of the foregoing.

[Claim 3]

A compound according to claim 1 or 2, a salt of the compound, or a hydrate of the foregoing, wherein Y represents an oxygen atom.

20 [Claim 4]

A compound according to any of claims 1 to 3, a salt

of the compound, or a hydrate of the foregoing, wherein one of X_1 and X_2 represents a group represented by the formula $-CH=$ and the other represent a nitrogen atom.

[Claim 5]

5 A compound according to any of claims 1 to 3, a salt of the compound, or a hydrate of the foregoing, wherein both X_1 and X_2 represent a group represented by the formula $-CH=$.

[Claim 6]

10 A compound according to any of claims 1 to 5, a salt of the compound, or a hydrate of the foregoing, wherein R_3 , R_4 , R_5 , R_6 and R_8 each represent a hydrogen atom, and R_7 represents a hydrogen atom, a halogen atom or an optionally substituted C_{1-6} alkyl group.

[Claim 7]

15 A compound according to any of claims 1 to 6, a salt of the compound, or a hydrate of the foregoing, wherein R_9 represents a group represented by the formula $-NHR_{17}$ (wherein R_{17} represents a C_{1-6} alkyl group, a C_{3-8} cycloalkyl group or a C_{6-10} aryl group).

20 [Claim 8]

 A compound according to any of claims 1 to 7, a salt of the compound, or a hydrate of the foregoing, wherein R_3 , R_4 , R_5 , R_6 , R_7 and R_8 each represent a hydrogen atom.

[Claim 9]

25 A compound according to any of claims 1 to 8, a salt of the compound, or a hydrate of the foregoing, wherein R_2

represents a hydrogen atom.

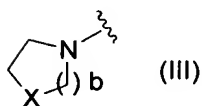
[Claim 10]

A compound according to any of claims 1 to 9, a salt of the compound, or a hydrate of the foregoing, wherein R_9 represents a group represented by the formula $-NH(CH_3)$.

[Claim 11]

A compound according to any of claims 1 to 10, a salt of the compound, or a hydrate of the foregoing, wherein R_1 represents a further optionally substituted group represented by the formula:

[chemical formula 7]

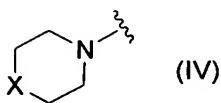


(wherein b represents 1 or 2; and X represents the same definition as X in claim 1).

[Claim 12]

A compound according to any of claims 1 to 11, a salt of the compound, or a hydrate of the foregoing, wherein R_1 represents a group represented by the formula:

[chemical formula 8]



(wherein X represents the same definition as X in claim 1).

[Claim 13]

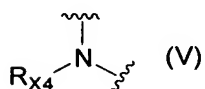
A compound according to claim 12, a salt of the compound, or a hydrate of the foregoing, wherein X in the formula (IV)

represents an oxygen atom.

[Claim 14]

A compound according to claim 12, a salt of the compound,
or a hydrate of the foregoing, wherein X in the formula (IV)
5 represents a group represented by the formula:

[chemical formula 9]

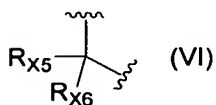


(wherein R_{X4} represents a hydrogen atom or a group represented
by the formula $-A_4-A_5-A_6$ (wherein A_4 and A_5 each independently
10 represent a single bond, an optionally substituted C_{1-6}
alkylene or a carbonyl group; and A_6 represents a hydrogen
atom, a C_{3-8} cycloalkyl group or a group represented by the
formula $-NR_{A4}R_{A5}$ or the formula $-OR_{A6}$ (wherein R_{A4} , R_{A5} and
 R_{A6} each independently represent a hydrogen atom or a C_{1-6}
15 alkyl group))).

[Claim 15]

A compound according to claim 12, a salt of the compound,
or a hydrate of the foregoing, wherein X in the formula (IV)
represents a group represented by the formula:

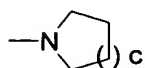
[chemical formula 10]



(wherein R_{X5} and R_{X6} each independently represent a hydrogen
atom or a group represented by the formula $-A_7-A_8-A_9$ (wherein
 A_7 and A_8 each independently represent a single bond, an

optionally substituted C₁₋₆ alkylene group or a carbonyl group; and A₉ represents a hydrogen atom, a C₃₋₈ cycloalkyl group, a group represented by the formula -NR_{A7}R_{A8}, or the formula -OR_{A9} (wherein R_{A7}, R_{A8}, and R_{A9} each independently represent a hydrogen atom or a C₁₋₆ alkyl group), or a group represented by the formula:

[chemical formula 11]



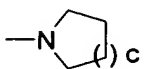
(wherein c represents 1 or 2)).

[Claim 16]

A compound according to claim 15, a salt of the compound, or a hydrate of the foregoing, wherein one of R_{x5} and R_{x6} in the formula (VI) represent a hydroxyl group and the other represents a hydrogen atom or a C₁₋₆ alkyl group.

[Claim 17]

A compound according to claim 15, a salt of the compound, or a hydrate of the foregoing, wherein one of R_{x5} or R_{x6} in the formula (VI) represents a hydrogen atom and the other represents a group represented by the formula:



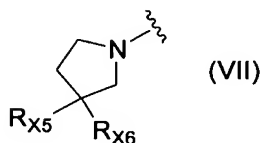
(wherein c represents 1 or 2).

[Claim 18]

A compound according to any of claims 1 to 10, a salt

of the compound, or a hydrate of the foregoing, wherein R_1 represents a group represented by the formula:

[chemical formula 13]

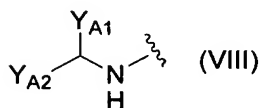


wherein R_{X5} and R_{X6} represent the same definitions as R_{X5} and R_{X6} in claim 15, respectively.

[Claim 19]

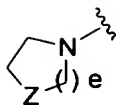
A compound according to any of claims 1 to 10, a salt of the compound, or a hydrate of the foregoing, wherein R_1 is a group represented by the formula:

[chemical formula 14]



(wherein Y_{A1} and Y_{A2} each independently represent a group represented by the formula $-A_{10}-A_{11}-A_{12}$ (wherein A_{10} represents a single bond or an optionally substituted C_{1-6} alkylene group; A_{11} represents a single bond, an oxygen atom, a carbonyl group, or a sulfonyl group; and A_{12} represents a hydrogen atom, a C_{1-6} alkyl group, a C_{6-10} aryl group, a group represented by the formula $-NR_{A10}R_{A11}$, or the formula $-OR_{A12}$ (wherein, R_{A10} , R_{A11} and R_{A12} each independently represent a hydrogen atom, a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group), or a group represented by the formula:

[chemical formula 15]

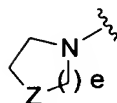


(wherein e represents 1 or 2; and Z represents an oxygen atom or a group represented by the formula $-CR_{X7}R_{X8}-$ or the formula $-NR_{X9}-$ (wherein R_{X7} , R_{X8} and R_{X9} each independently represent a hydrogen atom, a hydroxyl group or a C_{1-6} alkyl group)))).

[Claim 20]

A compound according to claim 19, a salt of the compound, or a hydrate of the foregoing, wherein one of Y_{A1} and Y_{A2} in the formula (VIII) represents a hydrogen and the other represents a group represented by the formula $-(CH_2)_2-A_{13}-A_{14}$ (wherein A_{13} represents a single bond, a carbonyl group or a sulfonyl group; and A_{14} represents a C_{1-6} alkyl group, a group represented by the formula $-NR_{A13}R_{A14}$ (wherein R_{A13} and R_{A14} each independently represent a hydrogen atom, a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group), or a group represented by the formula

[chemical formula 16]



(wherein e and Z represent the same definitions as e and Z in claim 19, respectively)).

[Claim 21]

A compound according to any of claims 1 to 20, a salt of the compound, or a hydrate of the foregoing, wherein the

compound is a compound selected from a group consisting of

(1) .

N1-ethyl-5-(2-((methoxylamino) carbonyl) amino-4-pyrimidy
1)oxy-1H-1-indolecarboxamide;

(2)

5-(6-(3-(3-diethylaminopropylamino)ureido)pyrimidin-4-y
loxy)-1H-indole-1-carboxylic acid methylamide;

(3)

5-(6-(((4-hydroxypiperidin-1-yl) carbonyl) amino)-pyrimid
in-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(4)

5-(6-((4-pyrrolidin-1-yl)piperidin-1-yl) carbonylamino)p
yrimidin-4-yloxy)-1H-indole-1-carboxylic acid
methylamide;

(5)

5-(2-(3-((1R)-1-carbamoyl-2-phenylethyl)ureido)pyridin-
4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(6)

5-(2-(3-((1S)-1-carbamoyl-2-phenylethyl)ureido)pyridin-
4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(7)

5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)pyridin-
4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(8)

5-(2-(3-(2-(4-hydroxy-4-methylpiperidin-1-yl)-2-oxoethy
l)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

methylamide;

(9)

5-(2-(3-((1S)-1-carbamoylethyl)ureido)pyridin-4-yloxy)-
1H-indole-1-carboxylic acid methylamide;

5 (10)

5-(2-(3-((1S)-1-carbamoyl-3-methylbutyl)ureido)pyridin-
4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(11)

10 5-(2-(3-carbamoylmethylureido)pyridin-4-yloxy)-1H-indol
e-1-carboxylic acid methylamide;

(12)

5-(2-(3-cyclopropylcarbamoylmethylureido)pyridin-4-ylox
y)-1H-indole-1-carboxylic acid methylamide;

(13)

15 5-(2-(3-((1S)-1-carbamoyl-2-hydroxyethyl)ureido)pyridin
-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(14)

5-(2-(3-((1R)-1-carbamoyl-2-hydroxyethyl)ureido)pyridin
-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

20 (15)

(2S)-2-(3-(4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridi
n-2-yl)ureido)-1,5-pentanedicarboxylic acid diamide;

(16)

25 (2S)-2-(3-(4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridi
n-2-yl)ureido)succinamide;

(17)

5-(2-(3-((1S)-1-cyclopropylcarbamoyl-2-hydroxyethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(18)

5 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(19)

10 5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(20)

15 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(21)

5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

20 (22)

5-(2-(3-((1S)-1-hydroxymethyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(23)

25 5-(2-(3-((1S)-1-hydroxymethyl-2-(morpholin-4-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

methanamide;

(24)

5-(2-(3-(2-cyclopropylcarbamoyl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methanamide;

5 (25)

5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methanamide;

(26)

10 5-(2-(3-(3-(4-hydroxy-4-methylpiperidin-1-yl)-3-oxopropyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methanamide;

(27)

N1-ethyl-5-(2-((2-ethoxyethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

15 (28)

N1-methyl-5-(2-((4-(2-hydroxy-2-methylpropionyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide ;

(29)

20 N1-methyl-5-(2-((3-(diethylamino)propylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(30)

N1-methyl-5-(2-((3-(4-hydroxypiperidino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

25 (31)

N1-methyl-5-(2-((3-(4-methylpiperazino)propyl)amino)ca

rbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(32)

5-(2-(3-(4-oxo-4-(pyrrolidin-1-yl)butyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

5 (33)

5-(2-(3-(3-(cyclopropylcarbamoyl)propyl)ureido)pyridin-4-yloxy)indole-1-carboxylic acid methylamide;

(34)

10 5-(2-(3-(4-(4-hydroxy-4-methylpiperidin-1-yl)-4-oxobutyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(35)

5-(2-(3-(3-(diethylcarbamoyl)propyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

15 (36)

5-(2-(3-(3-(methylcarbamoyl)propyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(37)

20 N1-methyl-5-(2-(pyrrolidin-1-ylcarbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(38)

N1-methyl-5-(2-(piperidin-1-ylcarbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(39)

25 N1-methyl-5-(2-((4-hydroxypiperidino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(40)

N1-methyl-5-(2-(4-oxopiperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(41)

5 5-(2-(((4-hydroxy-4-methylpiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(42)

10 N1-methyl-5-(2-((4-(1-hydroxy-1-methylethyl)piperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(43)

5-(2-(((4-(3-methylcarbamoylpropyl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

15 (44)

5-(2-(((4-(3-carbamoylpropyl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(45)

20 5-(2-((4-((pyrrolidin-1-yl)carbonyl)piperidin-1-yl)carbonylamino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide;

(46)

25 N1-methyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(47)

N1-methyl-5-(2-((4-(piperidin-1-yl)piperidin-1-yl) carbonyl) amino) pyridin-4-yloxy)-1H-1-indolecarboxamide;
(48)

5 N1-methyl-5-(2-((4-ethylpiperazino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
(49)

N1-methyl-5-(2-((4-(2-hydroxyethyl) piperazino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
(50)

10 N1-methyl-5-(2-((3-methylsulfonylpropylamino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
(51)

N1-methyl-5-(2-((4-(2-dimethylaminoacetyl) piperazino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
15 (52)

N1-methyl-5-(2-((4-cyclohexylpiperazino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
(53)

20 N4-(4-(1-(methylamino) carbonyl-1H-5-indolyl) oxy-2-pyridyl)-4-morpholinecarboxamide;
(54)

N1-methyl-5-(2-((1,1-dioxothiomorpholin-4-ylcarbonyl) amino) pyridin-4-yloxy)-1H-1-indolecarboxamide;
(55)

25 5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl) ureido) pyridin-4-yloxy)-1H-indole-1-carboxylic acid

ethylamide;

(56)

5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

5 ethylamide;

(57)

5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

ethylamide;

10 (58)

5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

ethylamide;

(59)

15 5-(2-(3-(2-(4-hydroxy-4-methylpiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

ethylamide;

(60)

N1-ethyl-5-(2-(((1-methyl-4-piperidyl)methyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

20

(61)

N1-ethyl-5-(2-(((2-diethylamino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(62)

25 N1-ethyl-5-(2-(((2-(morpholin-4-yl)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(63)

N1-ethyl-5-(2-(((2-(4-hydroxypiperidino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(64)

5 N1-methyl-5-(2-(((2-(4-hydroxypiperidino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(65)

N1-ethyl-5-(2-((3-(diethylamino)propylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

10 (66)

N1-ethyl-5-(2-((3-(morpholin-4-yl)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(67)

15 N1-ethyl-5-(2-((3-(4-methylpiperazino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(68)

N1-cyclopropyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

20 (69)

5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide;

(70)

25 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

cyclopropylamide;

(71)

5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide;

5 (72)

5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide;

(73)

10 5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide;

(74)

15 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide;

(75)

N1-phenyl-5-(2-(((3-(diethylamino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(76)

20 N1-phenyl-5-(2-(((3-(4-methylpiperazino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(77)

N1-ethyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

25 (78)

5-(2-(((4-hydroxy-4-methylpiperidin-1-yl)carbonyl)amino

)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide;
(79)

N1-ethyl-5-(2-((4-hydroxypiperidin-1-yl) carbonyl) amino-
4-pyridyl) oxy-1H-1-indolecarboxamide;
5 (80)

N1-ethyl-5-(2-(piperidin-1-yl carbonyl) amino-4-pyridyl) o
xy-1H-1-indolecarboxamide;
(81)

N1-ethyl-5-((2-((pyrrolidin-1-yl carbonyl) amino)-4-pyrid
10 yl) oxy)-1H-1-indolecarboxamide;
(82)

N4-(4-((1-(ethylamino) carbonyl-1H-5-indolyl) oxy)-2-pyri
dyl)-4-morpholinecarboxamide;
(83)

N1-ethyl-5-(2-((1,1-dioxothiomorpholin-4-yl carbonyl) ami
15 no)pyridin-4-yloxy)-1H-1-indolecarboxamide;
(84)

N1-ethyl-5-(2-((methoxylamino) carbonyl) amino-4-pyridyl)
oxy-1H-1-indolecarboxamide;
20 (85)

N1-cyclopropyl-5-(2-((4-hydroxypiperidino) carbonyl) amin
o-4-pyridyl) oxy-1H-1-indolecarboxamide;
(86)

N1-cyclopropyl-5-(2-((4-hydroxy-4-methylpiperidin-1-yl
25) carbonyl) amino)pyridin-4-yloxy)-1H-1-indolecarbox-amid
e;

(87)

N4-(4-(1-(cyclopropylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide;

(88)

5 N1-cyclopropyl-5-(2-((pyrrolidin-1-ylcarbonyl)amino)-4-pyridyl)oxy-1H-1-indolecarboxamide;

(89)

N1-cyclopropyl-5-(2-(piperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

10 (90)

N4-(4-(1-(cyclopentylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide;

(91)

15 5-(2-(((4-hydroxypiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopentylamide;

(92)

N1-cyclopentyl-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-ylcarbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(93)

20 N1-(3-methylbutyl)-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(94)

25 N1-(3-methylbutyl)-5-(2-((4-(hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(95)

N4-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide;

(96)

N1-(1-ethylpropyl)-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(97)

N1-(1-ethylpropyl)-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(98)

N4-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide;

(99)

N4-(4-(1-((1-pentyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide;

(100)

N1-(1-pentyl)-5-(2-(((4-hydroxypiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(101)

N1-(1-pentyl)-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(102)

N1-methyl-3-chloro-5-(2-(((3-(diethylamino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide;

(103)

N1-methyl-3-chloro-5-(2-((4-tetrahydro-1H-1-pyrrolyl)pip

eridino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxa
mide;

(104)

N1-methyl-3-chloro-5-(2-((4-hydroxypiperidino) carbonyl)
amino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(105)

N1-methyl-3-chloro-5-(2-(((3-(4-hydroxypiperidino) propy
l) amino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxa
mide;

(106)

N1-methyl-3-chloro-5-(2-((4-(2-hydroxyethyl) piperazino)
carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(107)

N4-(4-(3-chloro-1-(methylamino) carbonyl-1H-5-indolyl) ox
y-2-pyridyl)-4-morpholinecarboxamide;

(108)

N1-methyl-3-chloro-5-(2-((4-ethylpiperazino) carbonyl) am
ino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(109)

N1-ethyl-3-chloro-5-(2-((4-hydroxypiperidino) carbonyl) a
mino-4-pyridyl) oxy-1H-1-indolecarboxamide;

(110)

N1-ethyl-3-chloro-5-(2-(((3-(4-hydroxypiperidino) propyl
) amino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxam
ide;

(111)

N1-ethyl-3-chloro-5-(2-(((3-(diethylamino)propyl)amino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
(112)

5 N1,3-dimethyl-5-(2-((4-hydroxypiperidino) carbonyl) amino
-4-pyridyl) oxy-1H-1-indolecarboxamide;
(113)

N1,3-dimethyl-5-(2-((4-tetrahydro-1H-1-pyrrolylpiperidi
no) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide;
(114)

10 N1-cyclopropyl-5-(2-((4-hydroxypiperidino) carbonyl) amino
-4-pyridyl) oxy-3-methyl-1H-1-indolecarboxamide; and
(115)

N1-cyclopropyl-5-(2-((4-(2-hydroxyethyl)piperazino) carbo
nyl) amino-4-pyridyl) oxy-3-methyl-1H-1-indolecarboxamide
15 .

[Claim 22]

A compound according to any of claims 1 to 20, a salt
of the compound, or a hydrate of the foregoing, wherein the
compound is a compound selected from a group consisting of

20 (1)
5-(2-(((4-hydroxy-4-methylpiperidin-1-yl) carbonyl) amino
)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methanamide;

(2)

25 N1-methyl-5-(2-((4-hydroxypiperidino) carbonyl) amino-4-p
yridyl) oxy-1H-1-indolecarboxamide;

(3)

N1-methyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide;

(4)

5 N1-methyl-5-(2-(((4-(piperidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide; and

(5)

N4-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide.

10 [Claim 23]

A pharmaceutical composition comprising a compound according to any of claims 1 to 22 and a pharmaceutical adjuvant.

[Claim 24]

15 A prophylactic or therapeutic agent for a disease for which angiogenesis inhibition is effective, comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 25]

20 An angiogenesis inhibitor comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 26]

25 An antitumor agent comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 27]

An antitumor agent according to claim 26, wherein the tumor is a pancreatic cancer, a gastric cancer, a colon cancer, a breast cancer, a prostate cancer, a lung cancer, a renal cancer, a brain tumor, a blood cancer or an ovarian cancer.

[Claim 28]

A therapeutic agent for hemangioma comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 29]

A cancer metastasis inhibitor comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 30]

A therapeutic agent for retinal neovascularization or diabetic retinopathy comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 31]

A therapeutic agent for an inflammatory disease comprising as an active ingredient, a compound according to any of claims 1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 32]

A therapeutic agent for an inflammatory disease according to claim 31, wherein the inflammatory disease is

deformant arthritis, rheumatoid arthritis, psoriasis or
delayed hypersensitivity reaction.

[Claim 33]

5 A therapeutic agent for atherosclerosis comprising
as an active ingredient, a compound according to any of claims
1 to 22, a salt thereof, or a hydrate of the foregoing.

[Claim 34]

10 A prophylactic or therapeutic method for a disease
for which angiogenesis inhibition is effective, comprising
administering to a patient, a pharmacologically effective
dose of a compound according to any of claims 1 to 22, a
salt thereof, or a hydrate of the foregoing.

[Claim 35]

15 Use of a compound according to any of claims 1 to 22,
a salt thereof, or a hydrate of the foregoing for the
manufacture of a prophylactic or therapeutic agent for a
disease for which angiogenesis inhibition is effective.

[DETAILED DESCRIPTION OF THE INVENTION]

[0001]

20 [Technical Field to Which the Invention Belong]

The present invention relates to novel compounds
effective for prevention and treatment of various diseases
associated with abnormal angiogenesis, and to the medical
compositions such as angiogenesis inhibitors and antitumor
25 agents containing the novel compounds.

[0002]

[Prior Art]

Angiogenesis is an essential biological phenomenon for fetal vascular formation and morphological and functional development of organs. New blood vessels are assembled through several processes including endothelial cell migration, proliferation and tube formation, and the participation of mast cells, lymphocytes, interstitial cells and the like has been shown to be important in this process (J. Biol. Chem., 267, 10931, 1992).

A multiple *in vivo* angiogenesis-stimulating factors have been identified, particularly Vascular Endothelial Growth Factor (hereinafter abbreviated as "VEGF") and Fibroblast Growth Factor (hereinafter abbreviated as "FGF") are reported to enhance angiogenesis (Endocrinology, 133, 848, 1993, and Biochem. Biophys. Res. Commun., 147, 876, 1987).

Although physiological angiogenesis occurs at the time of healing of wound or in a female estrous cycle in adult individuals, it is known that pathological increase in angiogenesis in adult individuals is involved in onset or progression of various disease. Specific diseases associated with abnormal angiogenesis include cancer, rheumatoid arthritis, atherosclerosis, diabetic retinopathy, angioma, psoriasis, and the like (N. Engl. J. Med., 333, 1757, 1995). In particular, a literature has indicated angiogenesis dependency for solid tumor growth,

and angiogenesis inhibitors are therefore promising as new therapeutic agents for intractable solid tumors (J. Natl. Cancer Inst., 82, 4, 1990).

WO 02/16348 and WO 02/32872 are provided as prior arts with regard to 6-membered nitrogen-containing aromatic derivatives bonded with substituted indole.

Although WO 02/16348 describes indole derivatives which suppress VEGF-stimulated angiogenesis based on a selective tyrosine kinase inhibition, the pharmacological test results on their inhibition action are not disclosed. Although WO 02/32872 describes pyridine derivatives bonded with indole ring via an oxygen atom at the 4-position, neither the compound according to the present invention nor their inhibiting actions on FGF-stimulated angiogenesis are disclosed.

[0003]

[Problems to be Solved by the Invention]

It is an object of the present invention to investigate and discover angiogenesis-inhibiting compounds which: (1) exhibit antitumor activity by strongly suppressing both of angiogenesis included by VEGF and FGF which are major *in vivo* angiogenesis factors, (2) are highly useful as drug materials in terms of their properties, biokinetics and safety, and (3) are useful for amelioration, prevention and treatment of various diseases associated with abnormal increase in angiogenesis.

[0004]

[Means for Solving the Problem]

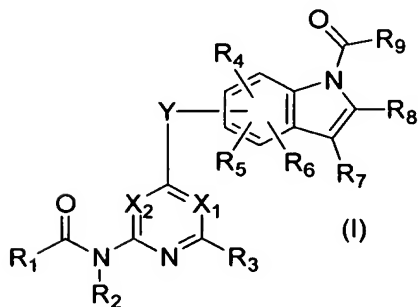
As a result of much diligent research in light of the circumstances described above, the present inventors have succeeded in synthesizing novel pyridine derivatives and pyrimidine derivatives represented by the following general formula (I), salts thereof, or hydrates of the foregoing. At the same time, the inventors have completed the present invention upon discovering that these compounds, the salts thereof, or the hydrates of the foregoing exhibit an excellent angiogenesis-inhibiting effect.

Specifically, the present invention provides the followings:

<1> a compound (except N1-cyclopropyl-5-((2-((2-chloroethylamino)carbonyl)amino)-4-pyridyl)oxy)-1H-1-indolecarboxamide) represented by the general formula:

[0005]

[chemical formula 17]



[0006]

wherein X₁ represents a nitrogen atom or a group represented

by the formula $-CR_{10}=$, X_2 represents a nitrogen atom or a group represented by the formula $-CR_{11}=$, and X_1 and X_2 do not represent a nitrogen atom at the same time;

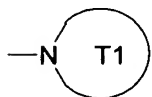
Y represents an oxygen atom, a sulfur atom, a sulfinyl group, a sulfonyl group, or a group represented by the formula $-NR_Y-$ (wherein R_Y represents a hydrogen atom or a C_{1-6} alkyl group);

R_1 represents an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-10} aryloxy group, a group represented by the formula $-NR_{12a}R_{12b}$, or a group represented

by the formula

[0007]

[chemical formula 18]



[0008]

(wherein $T1$ represents an optionally substituted 5- to 10-membered aromatic heterocycle which may have X in the ring or an optionally substituted 3- to 10-membered heterocycle which may have X in the ring);

R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_{10} and R_{11} each independently represent a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-8} cycloalkyl group, a group represented by the formula $-CO-R_{13}$, a group represented by the formula $-NR_{14}-CO-R_{13}$, a group represented by the formula

-SO₂-R₁₅, a group represented by the formula -NR₁₄-SO₂-R₁₅,
or a group represented by the formula -NR_{16a}R_{16b};

R₉ represents a group represented by the formula -NR_{16a}R_{16b}
or a group represented by the formula

5 [0009]
[chemical formula 19]



[0010]

(wherein T2 represents an optionally substituted 5- to 10-
10 membered aromatic heterocycle or an optionally substituted
3- to 10- membered heterocycle);

R_{12a} and R_{12b} each independently represent a hydrogen atom,
an optionally substituted C₁₋₆ alkyl group, an optionally
substituted C₃₋₆ alkenyl group, an optionally substituted
15 C₃₋₈ cycloalkyl group, an optionally substituted 3- to 10-
membered heterocyclic group, or an optionally substituted
C₁₋₆ alkoxy group;

R₁₃ represents a hydrogen atom, an optionally substituted
C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group,
20 an optionally substituted C₂₋₆ alkynyl group, an optionally
substituted C₃₋₈ cycloalkyl group, an optionally substituted
C₆₋₁₀ aryl group, an optionally substituted 5- to 10- membered
heteroaryl group, an optionally substituted 3- to 10-
membered heterocyclic group, an optionally substituted C₁₋₆
25 alkoxy group, an optionally substituted C₆₋₁₀ aryloxy group,

a group represented by the formula $-NR_{12a}R_{12b}$, or a group represented by the formula

[0011]

[chemical formula 20]



[0012]

(wherein T2 represents an optionally substituted 5- to 10-membered aromatic heterocycle or an optionally substituted 3- to 10- membered heterocycle);

10 R_2 and R_{14} each independently represent a hydrogen atom, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-8} cycloalkyl group, or a group represented by the formula $-CO-R_{13}$;

15 R_{15} represents an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted C_{6-10} aryl group, an optionally substituted 5- to 10- membered heteroaryl group, or an optionally substituted 3- to 10- membered heterocyclic group;

20

R_{16a} and R_{16b} each independently represent a hydrogen atom, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-6} alkenyl group, an optionally substituted C_{3-6} alkynyl group, an optionally substituted C_{3-8} cycloalkyl

25

group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted 5- to 10- membered heteroaryl group, an optionally substituted 3- to 10- membered heterocyclic group, or an optionally substituted C₁₋₆ alkoxy group; and

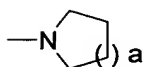
5 X represents an oxygen atom, a sulfur atom, a carbonyl group, a sulfonyl group, a group represented by the formula -CR_{X1}R_{X2}-, or a group represented by the formula -NR_{X3}- (wherein R_{X1}, R_{X2} and R_{X3} each independently represent a hydrogen atom or a group represented by the formula -A₁-A₂-A₃ (wherein A₁ and

10 A₂ each independently represent a single bond, an optionally substituted C₁₋₆ alkylene group or a carbonyl group; and A₃ represents a hydrogen atom, a C₃₋₈ cycloalkyl group, a group represented by the formula -NR_{A1}R_{A2}, or the formula -OR_{A3} (wherein, R_{A1}, R_{A2} and R_{A3} each independently represent a

15 hydrogen atom or a C₁₋₆ alkyl group), or an optionally substituted group represented by the formula

[0013]

[chemical formula 21]



[0014]

(wherein a represents 1 or 2))),

a salt thereof, or a hydrate of the foregoing;

<2> a compound (except

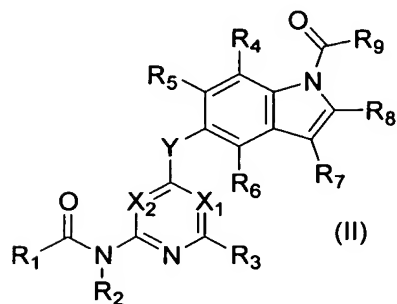
N1-cyclopropyl-5-((2-((2-chloroethylamino) carbonyl) amino)-4-pyridyl)oxy)-1H-1-indolecarboxamide) represented by

25

the general formula:

[0015]

[chemical formula 22]



5

[0016]

wherein X_1 , X_2 , Y , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 represent the same definitions as X_1 , X_2 , Y , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 in <1>, respectively,

a salt thereof, or a hydrate of the foregoing;

10

<3> a compound according to <1> or <2>, a salt of the compound, or a hydrate of the foregoing, wherein Y represents an oxygen atom;

<4> a compound according to any of <1> to <3>, a salt of the compound, or a hydrate of the foregoing, wherein one of X_1 and X_2 represents a group represented by the formula $-CH=$ and the other represent a nitrogen atom;

15

<5> a compound according to any of <1> to <3>, a salt of the compound, or a hydrate of the foregoing, wherein both X_1 and X_2 represent a group represented by the formula $-CH=$;

20

<6> a compound according to any of <1> to <5>, a salt of the compound, or a hydrate of the foregoing, wherein R_3 , R_4 , R_5 , R_6 and R_8 each represent a hydrogen atom, and R_7

represents a hydrogen atom, a halogen atom or an optionally substituted C₁₋₆ alkyl group;

<7> a compound according to any of <1> to <6>, a salt of the compound, or a hydrate of the foregoing, wherein R₉ represents a group represented by the formula -NHR₁₇ (wherein R₁₇ represents a C₁₋₆ alkyl group, a C₃₋₈ cycloalkyl group or a C₆₋₁₀ aryl group);

<8> a compound according to any of <1> to <7>, a salt of the compound, or a hydrate of the foregoing, wherein R₃, R₄, R₅, R₆, R₇ and R₈ each represent a hydrogen atom;

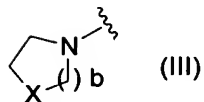
<9> a compound according to any of <1> to <8>, a salt of the compound, or a hydrate of the foregoing, wherein R₂ represents a hydrogen atom;

<10> a compound according to any of <1> to <9>, a salt of the compound, or a hydrate of the foregoing, wherein R₉ represents a group represented by the formula -NH(CH₃);

<11> a compound according to any of <1> to <10>, a salt of the compound, or a hydrate of the foregoing, wherein R₁ represents a further optionally substituted group represented by the formula:

[0017]

[chemical formula 23]



[0018]

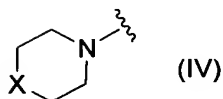
(wherein b represents 1 or 2; and X represents the same

definition as X in <1>);

<12> a compound according to any of <1> to <11>, a salt of the compound, or a hydrate of the foregoing, wherein R₁ represents a group represented by the formula:

5 [0019]

[chemical formula 24]



[0020]

(wherein X represents the same definition as X in <1>);

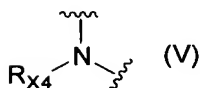
10 <13> a compound according to <12>, a salt of the compound, or a hydrate of the foregoing, wherein X in the formula (IV) represents an oxygen atom;

<14> a compound according to <12>, a salt of the compound, or a hydrate of the foregoing, wherein X in the formula (IV)

15 represents a group represented by the formula:

[0021]

[chemical formula 25]



[0022]

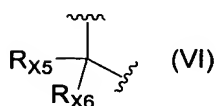
20 (wherein R_{X4} represents a hydrogen atom or a group represented by the formula -A₄-A₅-A₆ (wherein A₄ and A₅ each independently represent a single bond, an optionally substituted C₁₋₆ alkylene or a carbonyl group; and A₆ represents a hydrogen atom, a C₃₋₈ cycloalkyl group or a group represented by the

formula $-NR_{A4}R_{A5}$ or the formula $-OR_{A6}$ (wherein R_{A4} , R_{A5} and R_{A6} each independently represent a hydrogen atom or a C_{1-6} alkyl group)));

<15> a compound according to <12>, a salt of the compound, or a hydrate of the foregoing, wherein X in the formula (IV) represents a group represented by the formula:

[0023]

[chemical formula 26]

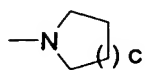


[0024]

(wherein R_{X5} and R_{X6} each independently represent a hydrogen atom or a group represented by the formula $-A_7-A_8-A_9$ (wherein A_7 and A_8 each independently represent a single bond, an optionally substituted C_{1-6} alkylene group or a carbonyl group; and A_9 represents a hydrogen atom, a C_{3-8} cycloalkyl group, a group represented by the formula $-NR_{A7}R_{A8}$, or the formula $-OR_{A9}$ (wherein R_{A7} , R_{A8} , and R_{A9} each independently represent a hydrogen atom or a C_{1-6} alkyl group), or a group represented by the formula:

[0025]

[chemical formula 27]



[0026]

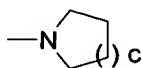
(wherein c represents 1 or 2));

<16> a compound according to <15>, a salt of the compound, or a hydrate of the foregoing, wherein one of R_{X5} and R_{X6} in the formula (VI) represent a hydroxyl group and the other represents a hydrogen atom or a C_{1-6} alkyl group;

5 <17> a compound according to <15>, a salt of the compound, or a hydrate of the foregoing, wherein one of R_{X5} or R_{X6} in the formula (VI) represents a hydrogen atom and the other represents a group represented by the formula:

[0027]

10 [chemical formula 28]



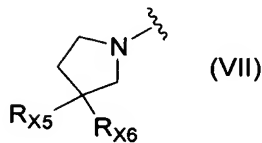
[0028]

(wherein c represents 1 or 2);

<18> a compound according to any of <1> to <10>, a salt of
15 the compound, or a hydrate of the foregoing, wherein R_1 represents a group represented by the formula:

[0029]

[chemical formula 29]



20 [0030]

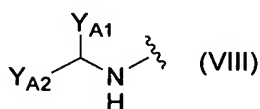
wherein R_{X5} and R_{X6} represent the same definitions as R_{X5} and R_{X6} in <15>, respectively;

<19> a compound according to any of <1> to <10>, a salt of

the compound, or a hydrate of the foregoing, wherein R_1 is a group represented by the formula:

[0031]

[chemical formula 30]

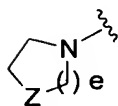


[0032]

(wherein Y_{A1} and Y_{A2} each independently represent a group represented by the formula $-A_{10}-A_{11}-A_{12}$ (wherein A_{10} represents a single bond or an optionally substituted C_{1-6} alkylene group; A_{11} represents a single bond, an oxygen atom, a carbonyl group, or a sulfonyl group; and A_{12} represents a hydrogen atom, a C_{1-6} alkyl group, a C_{6-10} aryl group, a group represented by the formula $-NR_{A10}R_{A11}$, or the formula $-OR_{A12}$ (wherein, R_{A10} , R_{A11} and R_{A12} each independently represent a hydrogen atom, a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group), or a group represented by the formula:

[0033]

[chemical formula 31]



[0034]

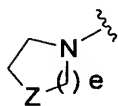
(wherein e represents 1 or 2; and Z represents an oxygen atom or a group represented by the formula $-CR_{X7}R_{X8}-$ or the formula $-NR_{X9}-$ (wherein R_{X7} , R_{X8} and R_{X9} each independently represent a hydrogen atom, a hydroxyl group or a C_{1-6} alkyl

group))));

<20> a compound according to <19>, a salt of the compound, or a hydrate of the foregoing, wherein one of Y_{A1} and Y_{A2} in the formula (VIII) represents a hydrogen and the other represents a group represented by the formula $-(CH_2)_2-A_{13}-A_{14}$ (wherein A_{13} represents a single bond, a carbonyl group or a sulfonyl group; and A_{14} represents a C_{1-6} alkyl group, a group represented by the formula $-NR_{A13}R_{A14}$ (wherein R_{A13} and R_{A14} each independently represent a hydrogen atom, a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group), or a group represented by the formula

[0035]

[chemical formula 32]



[0036]

(wherein e and Z represent the same definitions as e and Z in <19>, respectively));

<21> a compound according to any of <1> to <20>, a salt of the compound, or a hydrate of the foregoing, wherein the compound is a compound selected from a group consisting of

(1)

N1-ethyl-5-(2-((methoxylamino)carbonyl)amino-4-pyrimidin-1-yl)oxy-1H-indole-3-carboxamide,

(2)

5-(6-(3-(3-diethylaminopropylamino)ureido)pyrimidin-4-yl)

loxy)-1H-indole-1-carboxylic acid methylamide,

(3)

5-(6-(((4-hydroxypiperidin-1-yl)carbonyl)amino)-pyrimidin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

5 (4)

5-(6-((4-pyrrolidin-1-yl)piperidin-1-yl)carbonylamino)pyrimidin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(5)

10 5-(2-(3-((1R)-1-carbamoyl-2-phenylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(6)

5-(2-(3-((1S)-1-carbamoyl-2-phenylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

15 (7)

5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(8)

20 5-(2-(3-(2-(4-hydroxy-4-methylpiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(9)

5-(2-(3-((1S)-1-carbamoylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

25 (10)

5-(2-(3-((1S)-1-carbamoyl-3-methylbutyl)ureido)pyridin-

4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(11)

5-(2-(3-carbamoylmethylureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

5 (12)

5-(2-(3-cyclopropylcarbamoylmethylureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(13)

5-(2-(3-((1S)-1-carbamoyl-2-hydroxyethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

10

(14)

5-(2-(3-((1R)-1-carbamoyl-2-hydroxyethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(15)

(2S)-2-(3-(4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)ureido)-1,5-pentanedicarboxylic acid diamide,

15

(16)

(2S)-2-(3-(4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)ureido)succinamide,

20

(17)

5-(2-(3-((1S)-1-cyclopropylcarbamoyl-2-hydroxyethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(18)

5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

25

methylamide,

(19)

5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

5 methylamide,

(20)

5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

methylamide,

10 (21)

5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

methylamide,

(22)

15 5-(2-(3-((1S)-1-hydroxymethyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(23)

5-(2-(3-((1S)-1-hydroxymethyl-2-(morpholin-4-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

20 methylamide,

(24)

5-(2-(3-(2-cyclopropylcarbamoylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

25 (25)

5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)pyridin

-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(26)

5- (2- (3- (3- (4-hydroxy-4-methylpiperidin-1-yl)-3-oxopropyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(27)

N1-ethyl-5- (2- ((2-ethoxyethyl) amino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide,

(28)

10 N1-methyl-5- (2- ((4- (2-hydroxy-2-methylpropionyl) piperazino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide

(29)

15 N1-methyl-5- (2- ((3- (diethylamino) propylamino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide,

(30)

N1-methyl-5- (2- ((3- (4-hydroxypiperidino) propyl) amino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide,

(31)

20 N1-methyl-5- (2- ((3- (4-methylpiperazino) propyl) amino) carbonyl) amino-4-pyridyl) oxy-1H-1-indolecarboxamide,

(32)

5- (2- (3- (4-oxo-4- (pyrrolidin-1-yl) butyl) ureido) pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide,

(33)

5- (2- (3- (3- (cyclopropylcarbonyl) propyl) ureido) pyridin-

4-yloxy)indole-1-carboxylic acid methylamide,

(34)

5- (2- (3- (4- (4-hydroxy-4-methylpiperidin-1-yl)-4-oxobuty
1)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
5 methylamide,

(35)

5- (2- (3- (3- (diethylcarbamoyl)propyl)ureido)pyridin-4-yl
oxy)-1H-indole-1-carboxylic acid methylamide,

(36)

10 5- (2- (3- (3- (methylcarbamoyl)propyl)ureido)pyridin-4-ylo
xy)-1H-indole-1-carboxylic acid methylamide,

(37)

N1-methyl-5- (2- (pyrrolidin-1-ylcarbonyl) amino-4-pyridyl
)oxy-1H-1-indolecarboxamide,

15 (38)

N1-methyl-5- (2- (piperidin-1-ylcarbonyl) amino-4-pyridyl)
oxy-1H-1-indolecarboxamide,

(39)

20 N1-methyl-5- (2- ((4-hydroxypiperidino) carbonyl) amino-4-p
yridyl)oxy-1H-1-indolecarboxamide,

(40)

N1-methyl-5- (2- (4-oxopiperidin-1-ylcarbonyl) amino-4-pyr
idyl)oxy-1H-1-indolecarboxamide,

(41)

25 5- (2- (((4-hydroxy-4-methylpiperidin-1-yl) carbonyl) amino
)pyridin-4-yloxy)-1H-indole-1-carboxylic acid

methylamide,

(42)

N1-methyl-5-(2-((4-(1-hydroxy-1-methylethyl)piperidino)
carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

5 (43)

5-(2-(((4-(3-methylcarbamoylpropyl)piperidin-1-yl)carbo
nyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methylamide,

(44)

10 5-(2-(((4-(3-carbamoylpropyl)piperidin-1-yl)carbonyl)am
ino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methylamide,

(45)

15 5-(2-((4-((pyrrolidin-1-yl)carbonyl)piperidin-1-yl)carb
onylamino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methylamide,

(46)

N1-methyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)car
bonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

20 (47)

N1-methyl-5-(2-(((4-(piperidin-1-yl)piperidin-1-yl)carb
onyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(48)

25 N1-methyl-5-(2-((4-ethylpiperazino)carbonyl)amino-4-pyr
idyl)oxy-1H-1-indolecarboxamide,

(49)

N1-methyl-5-(2-((4-(2-hydroxyethyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(50)

5 N1-methyl-5-(2-((3-methylsulfonylpropylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(51)

N1-methyl-5-(2-((4-(2-dimethylaminoacetyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(52)

10 N1-methyl-5-(2-((4-cyclohexylpiperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(53)

15 N4-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,
(54)

N1-methyl-5-(2-((1,1-dioxothiomorpholin-4-ylcarbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,
(55)

20 5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide,
(56)

25 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide,
(57)

5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide,

(58)

5 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide,

(59)

10 5-(2-(3-(2-(4-hydroxy-4-methylpiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide,

(60)

N1-ethyl-5-(2-(((1-methyl-4-piperidyl)methyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

15 (61)

N1-ethyl-5-(2-(((2-diethylamino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(62)

20 N1-ethyl-5-(2-(((2-(morpholin-4-yl)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(63)

N1-ethyl-5-(2-(((2-(4-hydroxypiperidino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(64)

25 N1-methyl-5-(2-(((2-(4-hydroxypiperidino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(65)

N1-ethyl-5-(2-((3-(diethylamino)propylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(66)

5 N1-ethyl-5-(2-((3-(morpholin-4-yl)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(67)

N1-ethyl-5-(2-((3-(4-methylpiperazino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

10 (68)

N1-cyclopropyl-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(69)

15 5-(2-(3-((1R)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide,

(70)

20 5-(2-(3-((1S)-1-hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide,

(71)

5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide,

25 (72)

5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)pyridin

-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide,
(73)

5- (2- (3- ((1R)-1-hydroxymethyl-2-oxo-2-piperidin-1-yleth
yl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
5 cyclopropylamide,
(74)

5- (2- (3- ((1S)-1-hydroxymethyl-2-oxo-2-piperidin-1-yleth
yl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
cyclopropylamide,
10 (75)

N1-phenyl-5- (2- ((3- (diethylamino)propyl)amino)carbonyl
)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(76)

N1-phenyl-5- (2- ((3- (4-methylpiperazino)propyl)amino)ca
15 rbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(77)

N1-ethyl-5- (2- ((4- (pyrrolidin-1-yl)piperidin-1-yl)carb
onyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,
(78)

5- (2- ((4-hydroxy-4-methylpiperidin-1-yl)carbonyl)amino
20)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide,
(79)

N1-ethyl-5- (2- ((4-hydroxypiperidin-1-yl)carbonyl)amino-
4-pyridyl)oxy-1H-1-indolecarboxamide,
25 (80)

N1-ethyl-5- (2- (piperidin-1-ylcarbonyl)amino-4-pyridyl)o

xy-1H-1-indolecarboxamide,

(81)

N1-ethyl-5-((2-((pyrrolidin-1-ylcarbonyl)amino)-4-pyridyl)oxy)-1H-1-indolecarboxamide,

5 (82)

N4-(4-((1-(ethylamino)carbonyl-1H-5-indolyl)oxy)-2-pyridyl)-4-morpholinecarboxamide,

(83)

N1-ethyl-5-(2-((1,1-dioxothiomorpholin-4-ylcarbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

10

(84)

N1-ethyl-5-(2-((methoxylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(85)

15

N1-cyclopropyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(86)

N1-cyclopropyl-5-(2-(((4-hydroxy-4-methylpiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarbox-amid

20

e,

(87)

N4-(4-(1-(cyclopropylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,

(88)

25

N1-cyclopropyl-5-(2-((pyrrolidin-1-ylcarbonyl)amino)-4-pyridyl)oxy-1H-1-indolecarboxamide,

(89)

N1-cyclopropyl-5-(2-(piperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(90)

5 N4-(4-(1-(cyclopentylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,

(91)

5-(2-(((4-hydroxypiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopentylamide,

10 (92)

N1-cyclopentyl-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-ylcarbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(93)

15 N1-(3-methylbutyl)-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(94)

N1-(3-methylbutyl)-5-(2-((4-(hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

20 (95)

N4-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,

(96)

25 N1-(1-ethylpropyl)-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(97)

N1-(1-ethylpropyl)-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(98)

5 N4-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,

(99)

N4-(4-(1-((1-pentyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,

10 (100)

N1-(1-pentyl)-5-(2-((4-hydroxypiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(101)

15 N1-(1-pentyl)-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,

(102)

N1-methyl-3-chloro-5-(2-((3-(diethylamino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(103)

20 N1-methyl-3-chloro-5-(2-((4-tetrahydro-1H-1-pyrrolylpiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(104)

25 N1-methyl-3-chloro-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(105)

N1-methyl-3-chloro-5-(2-(((3-(4-hydroxypiperidino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(106)

5 N1-methyl-3-chloro-5-(2-((4-(2-hydroxyethyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(107)

N4-(4-(3-chloro-1-(methylanino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide,

10 (108)

N1-methyl-3-chloro-5-(2-((4-ethylpiperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(109)

15 N1-ethyl-3-chloro-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(110)

N1-ethyl-3-chloro-5-(2-(((3-(4-hydroxypiperidino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

20 (111)

N1-ethyl-3-chloro-5-(2-(((3-(diethylamino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(112)

25 N1,3-dimethyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,

(113)

N1,3-dimethyl-5-(2-((4-tetrahydro-1H-1-pyrrolyl)piperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(114)

N1-cyclopropyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-3-methyl-1H-1-indolecarboxamide, and
(115)

N1-cyclopropyl-5-(2-((4-(2-hydroxyethyl)piperazino)carbonyl)amino-4-pyridyl)oxy-3-methyl-1H-1-indolecarboxamide
;

<22> a compound according to any of <1> to <20>, a salt of the compound, or a hydrate of the foregoing, wherein the compound is a compound selected from a group consisting of
(1)

5-(2-(((4-hydroxy-4-methylpiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methanamide,
(2)

N1-methyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide,
(3)

N1-methyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide,
(4)

N1-methyl-5-(2-(((4-(piperidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide, and
(5)

N4-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide;

<23> a pharmaceutical composition comprising a compound according to any of <1> to <22> and a pharmaceutical adjuvant;

5 <24> a prophylactic or therapeutic agent for a disease for which angiogenesis inhibition is effective, comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

10 <25> an angiogenesis inhibitor comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<26> an antitumor agent comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

15 <27> an antitumor agent according to <26>, wherein the tumor is a pancreatic cancer, a gastric cancer, a colon cancer, a breast cancer, a prostate cancer, a lung cancer, a renal cancer, a brain tumor, a blood cancer or an ovarian cancer;

20 <28> a therapeutic agent for hemangioma comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<29> a cancer metastasis inhibitor comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

25 <30> a therapeutic agent for retinal neovascularization or diabetic retinopathy comprising as an active ingredient,

a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<31> a therapeutic agent for an inflammatory disease comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<32> a therapeutic agent for an inflammatory disease according to <31>, wherein the inflammatory disease is deformatant arthritis, rheumatoid arthritis, psoriasis or delayed hypersensitivity reaction;

<33> a therapeutic agent for atherosclerosis comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<34> an angiogenesis inhibition-based antitumor agent comprising as an active ingredient, a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<35> a prophylactic or therapeutic method for a disease for which angiogenesis inhibition is effective, comprising administering to a patient, a pharmacologically effective dose of a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing;

<36> use of a compound according to any of <1> to <22>, a salt thereof, or a hydrate of the foregoing for the manufacture of a prophylactic or therapeutic agent for a disease for which angiogenesis inhibition is effective.

[0037]

The meanings of the terms, symbols or the like used in the specification are described and the present invention is described in detail below.

5 [0038]

It should be noted that, although the structural formula of a compound may indicate a certain isomer for convenience's sake in this specification, the present invention include all geometrical isomers generated in the structures of compounds, isomers such as optical isomers based on asymmetric carbon atom, stereoisomers and tautomers, and a mixture of isomers, which are not limited to the descriptions of formulas for convenience's sake, either of isomers or mixtures may be included. Therefore, although optically active compounds and racemic compounds may be existent when they have asymmetric carbon atoms in a molecule, they are not particularly limited in the present invention and any cases are included. In addition, although a variety of crystal morphism are existent, these are not limited similarly. Specifically, any of a single crystal form or mixtures may be included, in addition, anhydrides or hydrates may be included.

10
15
20

In addition, compounds according to the present invention also include compounds which still indicate a desired activity after they are subjected to metabolism such as oxidation, reduction, hydrolysis and conjugation in an

25

organism, and the present invention also include compounds which produce the compounds according to the present invention after they are subjected to metabolism such as oxidation, reduction and hydrolysis.

5 [0039]

The term "C₁₋₆ alkyl group" as described in the specification represents a linear or branched alkyl group of 1 to 6 carbon atoms, which is a monovalent group derived by removing a hydrogen atom from an aliphatic hydrocarbon of 1 to 6 carbon atoms. As specific examples there may be mentioned methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, sec-butyl group, t-butyl group, n-pentyl group, i-pentyl group, sec-pentyl group, neopentyl group, 1-methylbutyl group, 15 2-methylbutyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, n-hexyl group, i-hexyl group, 1-methylpentyl group, 2-methylpentyl group, 3-methylpentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 2,2-dimethylbutyl group, 1,3-dimethylbutyl group, 20 2,3-dimethylbutyl group, 3,3-dimethylbutyl group, 1-ethylbutyl group, 2-ethylbutyl group, 1,1,2-trimethylpropyl group, 1,2,2-trimethylpropyl group, 1-ethyl-1-methylpropyl group, 1-ethyl-2-methylpropyl group or the like, and preferably methyl group, ethyl group, 25 n-propyl group, i-propyl group, n-butyl group, i-butyl group, sec-butyl group and t-butyl group.

[0040]

The term "C₂₋₆ alkenyl group" as described in the specification represents a linear or branched alkenyl group of 2 to 6 carbon atoms which may contain 1 to 2 double bonds.

5 As specific examples there may be mentioned ethenyl group, 1-propenyl group, 2-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-1-propenyl group, pentenyl group, hexenyl group, hexandienyl group or the like, and preferably ethenyl group, 1-propenyl group, 10 2-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group and 2-methyl-1-propenyl group.

[0041]

The term "C₂₋₆ alkynyl group" as described in the specification represents a linear or branched alkynyl group of 2 to 6 carbon atoms which may contain 1 to 2 triple bonds.

15 As specific examples there may be mentioned ethynyl group, 1-propynyl group, 2-propynyl group, 1-butyngyl group, 2-butyngyl group, 3-butyngyl group, pentynyl group, hexynyl group, hexandiynyl group or the like, and preferably ethynyl group, 1-propynyl group, 2-propynyl group, 1-butyngyl group, 20 2-butyngyl group and 3-butyngyl group.

[0042]

The term "C₃₋₈ cycloalkyl group" as described in the specification represents a cyclic aliphatic hydrocarbon group of 3 to 8 carbon atoms, and as specific examples there 25 may be mentioned cyclopropyl group, cyclobutyl group,

cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group or the like, and preferably cyclopropyl group, cyclobutyl group and cyclopentyl group.

[0043]

5 The term "C₁₋₆ alkylene group" as described in the specification represents a divalent group derived by further removing a hydrogen atom from the aforementioned definition of "C₁₋₆ alkyl group." As specific examples there may be mentioned methylene group, ethylene group, methylethylene group, propylene group, ethylethylene group, 10 1,1-dimethylethylene group, 1,2-dimethylethylene group, tetramethylene group, pentamethylene group, hexamethylene group or the like, and preferably methylene group and ethylene group.

15 [0044]

 The term "C₁₋₆ alkoxy group" as described in the specification represents an oxy group bonded with the aforementioned definition of "C₁₋₆ alkyl group." As specific examples there may be mentioned methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, t-butoxy group, 20 n-pentyloxy group, i-pentyloxy group, sec-pentyloxy group, neopentyloxy group, 1-methylbutoxy group, 2-methylbutoxy group, 1,1-dimethylpropoxy group, 1,2-dimethylpropoxy group, n-hexyloxy group, i-hexyloxy group, 25 1-methylpentyloxy group, 2-methylpentyloxy group,

3-methylpentyloxy group, 1,1-dimethylbutoxy group,
 1,2-dimethylbutoxy group, 2,2-dimethylbutoxy group,
 1,3-dimethylbutoxy group, 2,3-dimethylbutoxy group,
 3,3-dimethylbutoxy group, 1-ethylbutoxy group,
 5 2-ethylbutoxy group, 1,1,2-trimethylpropoxy group,
 1,2,2-trimethylpropoxy group, 1-ethyl-1-methylpropoxy
 group, 1-ethyl-2-methylpropoxy group or the like, and
 preferably methoxy group, ethoxy group, n-propoxy group,
 i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy
 10 group, and t-butoxy group.

[0045]

The term "C₁₋₆ alkylthio group" as described in the
 specification represents a thio group bonded with the
 aforementioned definition of "C₁₋₆ alkyl group." As
 15 specific examples there may be mentioned methylthio group,
 ethylthio group, n-propylthio group, i-propylthio group,
 n-buthylthio group, i-buthylthio group, sec-buthylthio
 group, t-buthylthio group, n-pentylthio group,
 i-pentylthio group, sec-pentylthio group, neopentylthio
 20 group, 1-methylbutylthio group, 2-methylbutylthio group,
 1,1-dimethylpropylthio group, 1,2-dimethylpropylthio
 group, n-hexylthio group, i-hexylthio group,
 1-methylpentylthio group, 2-methylpentylthio group,
 3-methylpentylthio group, 1,1-dimethylbutylthio group,
 25 1,2-dimethylbutylthio group, 2,2-dimethylbutylthio group,
 1,3-dimethylbutylthio group, 2,3-dimethylbutylthio group,

3,3-dimethylbutylthio group, 1-ethylbutylthio group,
2-ethylbutylthio group, 1,1,2-trimethylpropylthio group,
1,2,2-trimethylpropylthio group,
1-ethyl-1-methylpropylthio group,
5 1-ethyl-2-methylpropylthio group or the like, and
preferably methylthio group, ethylthio group, n-propylthio
group, i-propylthio group, n-butylthio group, i-butylthio
group, sec-butylthio group and t-butylthio group.

[0046]

10 The term "C₆₋₁₀ aryl group" as described in the
specification represents an aromatic hydrocarbon ring group
of 6 to 10 carbon atoms. As specific examples there may
be mentioned phenyl group, 1-naphtyl group, 2-naphtyl group,
indenyl group, azulenyl group, heptalenyl group or the like,
15 and preferably phenyl group, 1-naphthyl group and 2-naphtyl
group.

[0047]

The term "C₆₋₁₀ aryloxy group" as described in the
specification represents an oxy group bonded with the
20 aforementioned definition of "C₆₋₁₀ aryl group." As specific
examples there may be mentioned phenoxy group, 1-naphthyloxy
group, 2-naphthyloxy group, indenyloxy group, azulenyloxy
group, heptalenyloxy group or the like, and preferably
phenoxy group, 1-naphthyloxy group and 2-naphthyloxy group.

25 [0048]

The term "halogen atom" as described in the

specification represents fluorine atom, chlorine atom, bromine atom or iodine atom, and preferably fluorine atom, chlorine atom and bromine atom.

[0049]

5 The term "heteroatom" as described in the specification represents nitrogen atom, sulfur atom, or oxygen atom.

[0050]

10 The term "5- to 10- membered aromatic heterocycle" as described in the specification represents an aromatic ring in which the number of atoms forming the ring is 5 to 10, and 1 to a plurality of heteroatoms are contained in the atoms forming the ring. Specific examples are pyrrole ring, pyridine ring, pyridazine ring, pyrimidine ring, 15 pyrazine ring, pyrazole ring, imidazole ring, triazole ring, tetrazole ring, indole ring, isoindole ring, indazole ring, quinoline ring, isoquinoline ring, cinnoline ring, quinazoline ring, quinoxaline ring, naphthyridine ring, phthalazine ring, carbazole ring, purine ring, furan ring, 20 thiophene ring, benzimidazole ring, imidazopyridine ring, imidazotriazine ring, pyrrolopyridine ring, pyrrolopyrimidine ring, pyridopyrimidine ring, oxazole ring, isooxazole ring, thiazole ring, isothiazole ring, phenoxazine ring, phenothiazine ring, furopyrrole ring, 25 imidazothiazole ring, benzoxazole ring, benzthiazole ring, pyrazoloxazole ring, pyridoxazine ring, benzofuran ring,

benzothiophene ring or the like.

[0051]

The term "5- to 10- membered heteroaryl group" as described in the specification represents a monovalent group derived by removing a hydrogen atom from the aforementioned definition of "5- to 10- membered aromatic heterocycle."

[0052]

The term "3- to 10- membered heterocycle" as described in the specification represents,

- (1) a monocyclic or bicyclic non-aromatic ring
- (2) having 3 to 10 atoms in the ring,
- (3) containing 1 to 2 hetero atoms among the atoms of the ring,
- (4) optionally including 1 to 2 double bonds in the ring,
- and
- (5) optionally including 1 to 3 carbonyl groups in the ring.

Specific examples are aziridine ring, azetidine ring, pyrrolidine ring, piperidine ring, homopiperidine ring, piperazine ring, homopiperazine ring, morpholine ring, thiomorpholine ring, pyridone ring, phthalimide ring, succinimide ring or the like, and preferably azetidine ring, pyrrolidine ring, piperidine ring, piperazine ring, morpholine ring and thiomorpholine ring.

[0053]

The term "3- to 10- membered heterocyclic group" as described in the specification represents a monovalent group

derived by removing a hydrogen atom from the aforementioned definition of "3- to 10- membered heterocycle."

[0054]

The term "optionally substituted" as described in the specification is equivalent in the meaning as in "which may have 1 or a plurality of substitutes by arbitrarily combining them at substitutable positions". As specific examples of such substituents there may be mentioned the following:

- (1) a halogen atom,
- (2) a hydroxyl group,
- (3) a thiol group,
- (4) a nitro group,
- (5) a cyano group,
- (6) an azido group,
- (7) a formyl group,
- (8) a carboxyl group,
- (9) an amino group, or
- (10) a group represented by the formula $-T^1-T^2-T^3$, wherein T^1 represents a single bond or a C_{1-6} alkylene group; T^2 represents a single bond, a C_{1-6} alkylene group, an oxygen atom, an sulfur atom, a sulfinyl group, a sulfonyl group, a carbonyl group, or a group represented by the formula $-O-CO-$, the formula $-CO-O-$, the formula $-NR^{T1}-$, the formula $-CO-NR^{T1}-$, the formula $-NR^{T1}-CO-$, the formula $-SO_2-NR^{T1}-$, or the formula $-NR^{T1}-SO_2-$; T^3 each independently represents a hydrogen atom, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group,

a C₃₋₈ cycloalkyl group, a C₆₋₁₀ aryl group, a 5- to 10- membered heteroaryl group, a 3- to 10- membered heterocyclic group or a group represented by the formula -N(R^{T2})(R^{T3}); R^{T1}, R^{T2}, or R^{T3} each independently represent a hydrogen atom or a C₁₋₆ alkyl group; wherein a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₈ cycloalkyl group, a C₆₋₁₀ aryl group, a 5- to 10- membered heteroaryl group and a 3- to 10- membered heterocyclic group in T³ may each independently have 1 to 3 groups selected from a group of the below-mentioned substituent group;

<Substituent Group>

a halogen atom, a hydroxyl group, a thiol group, a nitro group, a cyano group, a C₁₋₆ alkyl group, a C₃₋₈ cycloalkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₆₋₁₀ aryl group, a 5- to 10- membered heteroaryl group, a 3- to 10- membered heterocyclic group, a C₁₋₆ alkoxy group and a C₁₋₆ alkylthio group.

[0055]

The term "leaving group" as described in the specification may be any group commonly known as a leaving group in organic synthesis, with no special restrictions, and as specific examples there may be mentioned a halogen atom such as a chlorine atom, a bromine atom, an iodine atom; a nitro group; an alkylthio group such as a methylthio group, an ethylthio group and a propylthio group; an arylthio group such as a phenylthio group, a toluythio group and a

2-pyridylthio group; an alkylsulfonyloxy group such as a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, an ethanesulfonyloxy group, a propanesulfonyloxy; an arylsulfonyloxy group such as a benzenesulfonyloxy group, a p-toluenesulfonyloxy group; an alkanoyloxy group such as an acetoxy group and a trifluoroacetoxy group; an alkoxy group such as a methoxy group, an ethoxy group and a propoxy group; an alkylamino group such as a methylamino group, an ethylamino group, a propylamino group and a butylamino group; a dialkylamino group such as a dimethylamino group, a diethylamino group, a dipropylamino group, a methylethylamino group, an ethylpropylamino group and a methylpropylamino group; a substituted phosphoryloxy group such as diphenoxyphosphoryloxy group or the like, and preferably a halogen atom such as a chlorine atom, a bromine atom and an iodine atom, a trifluoromethanesulfonyl group or the like.

[0056]

As a "salt" described in the specification, there may be mentioned, for example, a salt with inorganic acid, a salt with organic acid, a salt with inorganic base, a salt with organic base, a salt with acidic or basic amino acid or the like, preferably a pharmacologically acceptable salt. A salt is formed in an appropriate ratio of 0.1 to 5 molecules of acid or base to one molecule of the compound.

As preferable examples of a salt with inorganic acid,

there may be mentioned, for example, a salt with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid phosphoric acid, or the like, and as preferable examples of a salt with organic acid, there may be mentioned, for example, a salt with acetic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, lactic acid, stearic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid or the like.

As preferable examples of a salt with inorganic base, there may be mentioned, for example, an alkali metal salt such as a sodium salt and a potassium salt, an alkali earth metal salt such as a calcium salt and a magnesium salt, an aluminum salt, an ammonium salt or the like. As preferable examples of a salt with organic base, there may be mentioned, for example, a salt with diethylamine, diethanolamine, meglumine, N,N'-dibenzylethylenediamine or the like.

As preferable examples of a salt with acidic amino acid, there may be mentioned, for example, a salt with aspartic acid, glutamic acid or the like, and as preferable examples of a salt with basic amino acid, there may be mentioned, for example, a salt with arginine, lysine, ornithine or the like.

[0057]

As a "adjuvant" described in the specification, there may be mentioned, for example, an excipient, a binder, a disintegrator, a lubricant, a coloring agent, a corrective

coating, a stabilizer, a emulsifier, a absorbefacient, a
surfactant, a pH adjustor, a preservative, an antioxidant
or the like.

[0058]

5 [Embodiment]

Production methods for the compounds of the invention
will now be described. Various methods may be considered
for production of compounds of the invention represented
by the general formulas (I) and (II) with synthesis carried
out by ordinary organic synthesis means, and the following
are representative examples of methods for their production.

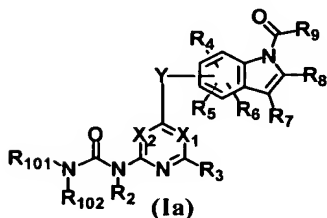
[General synthesis method]

[Production method 1]

A typical production method of the compound represented by
the formula (Ia)

[0059]

[chemical formula 33]

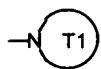


[0060]

wherein, R₁₀₁, R₁₀₂ may represent the same definitions as the
formula R_{12a}, R_{12b} (R_{12a} and R_{12b} represent the same definitions
as the aforementioned definition), respectively; or R₁₀₁ and
R₁₀₂ form a ring, and the formula -NR₁₀₁R₁₀₂ may represent the

same definition as the formula

[chemical formula 34]



[0061]

5 (wherein T1 represents the same definition as the
aforementioned definition); other symbols represent the
same definitions as the aforementioned definitions.

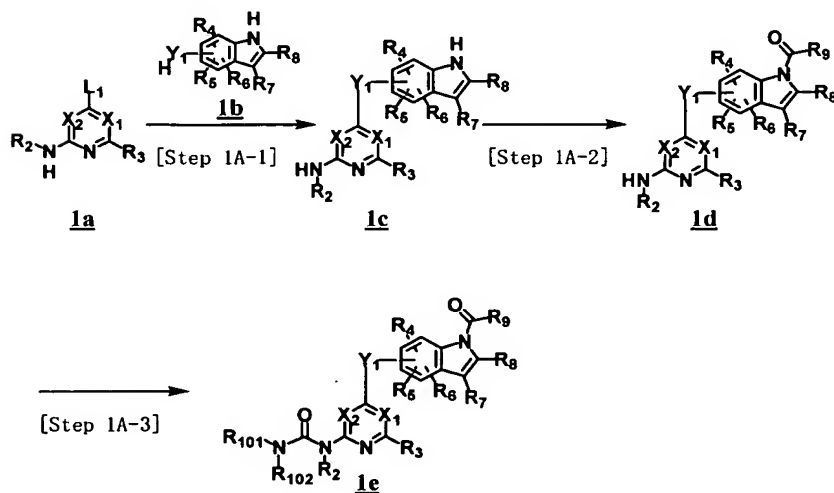
[0062]

[Production method 1-A]

10 A typical production method of the compound (1e), which is
the compounds represented by the formula (1a), wherein Y
represents an oxygen atom, a sulfur atom or a group
represented by the formula -NR_Y- (R_Y represents a hydrogen
atom or a C₁₋₆ alkyl group)

15 [0063]

[chemical formula 35]



[0064]

wherein, Y_1 represents an oxygen atom, a sulfur atom or a group represented by the formula $-NR_Y-$ (R_Y represents a hydrogen atom or a C_{1-6} alkyl group); L_1 represents a leaving group; other symbols represent the same definitions as the
5 aforementioned definition.

<Step 1A-1>

This is a step for obtaining a compound (1c) by
condensing pyrimidine or a pyrimidine derivative (1a) having
a leaving group (L_1) at the 4-position with an indole
10 derivative (1b). As a reaction solvent,
N-methylpyrrolidone, N,N-dimethylformamide, dimethyl
sulfoxide, 2-ethoxyethanol, chlorobenzene or the like can
be used. A base or an acid may be added thereto, specifically,
an organic base such as diisopropylethylamine, an inorganic
15 base such as potassium carbonate, cesium carbonate and sodium
hydroxide and an acid such as pyridine hydrochloride and
hydrochloric acid can be used. The reaction can be performed
at a temperature ranging from room temperature to reflux
temperature for a reaction time ranging from 10 minutes to
20 30 hours. In addition, a compound where a halogen atom which
is not as a leaving group is bonded on pyrimidine or pyridine
ring may be used as a starting material, and the halogen
atom can be reduced by the catalytic reduction method or
the like after this step.

25 <Step 1A-2>

This is a step for obtaining a compound (1d) by

carboxyamidating the 1-position of an indole derivative (1c).

As a reagent, a carbamate derivative, an isocyanate derivative, a halogenated carbamoyl derivative or the like can be used. As a reaction solvent, chloroform, toluene, N-methylpyrrolidone, N,N-dimethylformamide, dimethyl sulfoxide, chlorobenzene can be used. A base may be added thereto, specifically, an organic base such as pyridine, triethylamine and diisopropylethylamine, an inorganic base such as potassium carbonate, cesium carbonate and sodium hydride can be used, for example. The reaction can be performed for a time of 10 minutes to 30 hours at a temperature of 0 °C to reflux temperature.

<Step 1A-3>

This is a step for converting a compound (1d) into a urea derivative (1e). Carbamate ester derivative is prepared by using phenyl chlorocarbonate or the like as a reagent, for example. After this intermediate is isolated, or not isolated, the intermediate is allowed to react with an amine, thereby a urea derivative can be obtained. Alternatively, by reacting a carbamate derivative or an isocyanate derivative as a reagent, a corresponding urea derivative can be converted into. As a reaction solvent, chloroform, toluene, N-methylpyrrolidone, N,N-dimethylformamide, dimethyl sulfoxide, chlorobenzene or the like can be used. A base may be added thereto, specifically, an organic base such as pyridine,

triethylamine, and diisopropylethylamine, an inorganic base such as potassium carbonate, cesium carbonate and sodium hydride can be used, for example. The reaction can be performed for a time of 10 minutes to 30 hours at a temperature of 0 °C to reflux temperature.

It should be noted that a substituent conversion in R_2 , R_{101} , R_{102} can be also performed by suitably using an oxidation reaction, a reduction reaction, a reductive amination reaction, an ester formation reaction, an amide formation reaction, a protecting group introduction reaction, a deprotection reaction, a hydrolysis reaction or the like which are generally used before and/or after each process. Specifically, for example, in the case that R_2 is a hydrogen atom in the compounds (1a), (1c) and (1d), the following methods come under the above-mentioned substituent conversions; that is, a method for converting R_2 into a C_{1-6} alkyl group by performing a reductive amination reaction with aldehyde or ketone, a method in which, after a corresponding urea derivative is obtained as in <Step 1A-3> from the compound (1c) and an amine having ketone or aldehyde, an amine side chain is introduced into R_{101} , R_{102} by further performing a reductive amination reaction with an amine, or the like. In these cases, sodium cyanoborohydride, sodium trimethoxyborohydride or the like can be used as a reducing agent, and methanol, tetrahydrofuran, dichloromethane, dichloroethane or the like can be used as

a reaction solvent. In addition, a method that a benzotriazole derivative is prepared and the derivative is reduced by sodium borohydride as reported in Tetrahedron 47, 2683 (1991), or the like is useful. Alternatively, a corresponding urea is formed as in <Step 1A-3> from the compound (1c) and an amine having an ester. After the ester is hydrolyzed by bases such as lithium hydroxide, sodium hydroxide or potassium hydroxide in aqueous ethanol, an amide derivative can be also obtained by using a condensing agent. In this case, N,N-dimethylformamide, tetrahydrofuran or the like can be used as a reaction solvent, and 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride, (1H-1,2,3-benzotriazole-1-yloxy)(tri(dimethylamino))phosphonium hexafluorophosphate can be used as a condensing agent. The reaction can be performed for a time of 10 minutes to 30 hours at a temperature of 0 °C to reflux temperature.

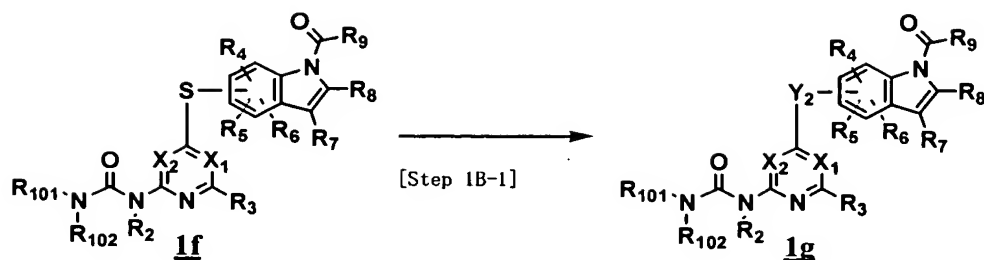
[0065]

[Production method 1-B]

A production method of the compound (1g), which is the compounds represented by the formula (Ia), wherein Y is a sulfinyl group or a sulfonyl group

[0066]

[chemical formula 36]



[0067]

wherein, Y₂ represents a sulfinyl group or a sulfonyl group;
other symbols represent the same definitions as
aforementioned definitions.

This is a step for oxidation of a compound (1f) to
a compound (1g). Hydrogen peroxide, peracetic acid,
methaperiodate, 3-chloroperbenzoic acid or the like can be
used as an oxidizing agent. Methanol, water,
dichloromethane, chloroform or the like can be used as a
solvent. The reaction can be performed for a time of 10
minutes to 30 hours at a temperature of 0 °C to reflux
temperature.

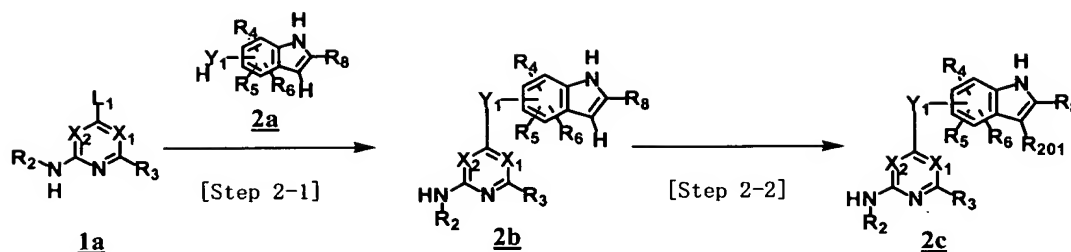
[0068]

[Production method 2]

Another production method of the compound (2c), which is
the compound (1c) having a halogen atom, a formyl group,
or a cyano group as a substituent at the 3-position in the
indole ring

[0069]

[chemical formula 37]



[0070]

wherein, R₂₀₁ represents a halogen atom, a formyl group or a cyano group; other symbols represent the same definitions as the aforementioned definitions.

<Step 2-1>

This is a step for obtaining a compound (2b) by the condensation of a pyrimidine or pyridine derivative (1a) and a indole derivative (2a) not having a substituent on the 3-position. The compound (2b) can be obtained under the same conditions as <Step 1A-1>.

<Step 2-2>

This is a step in which a substituent is introduced into 3-position of indole in a compound (2b) to obtain a compound substituted at the 3-position of indole (2c). A compound (2c) substituted with a halogen atom, a formyl group, an amino group or the like as the 3-position substituent can be obtained by reacting a compound (2b) with halogenation agents such as N-chlorosuccinimide, N-bromosuccinimide or a mixed reagent of phosphorous oxychloride or thionyl chloride with N,N-dimethylformamide, or after converting the compound into a N-chlorosulfonylcarbamoyl derivative

by allowing chlorosulfonyl isocyanate to react with the compound, followed by allowing triethylamine to react with the derivative or the like as reported in Tetrahedron 50, 6549 (1994). As a reaction solvent, 2-propanol, N,N-dimethylformamide, tetrahydrofuran, acetonitrile or the like can be used, and the reaction can be performed for a time of 10 minutes to 30 hours at a temperature of 0 °C to reflux temperature.

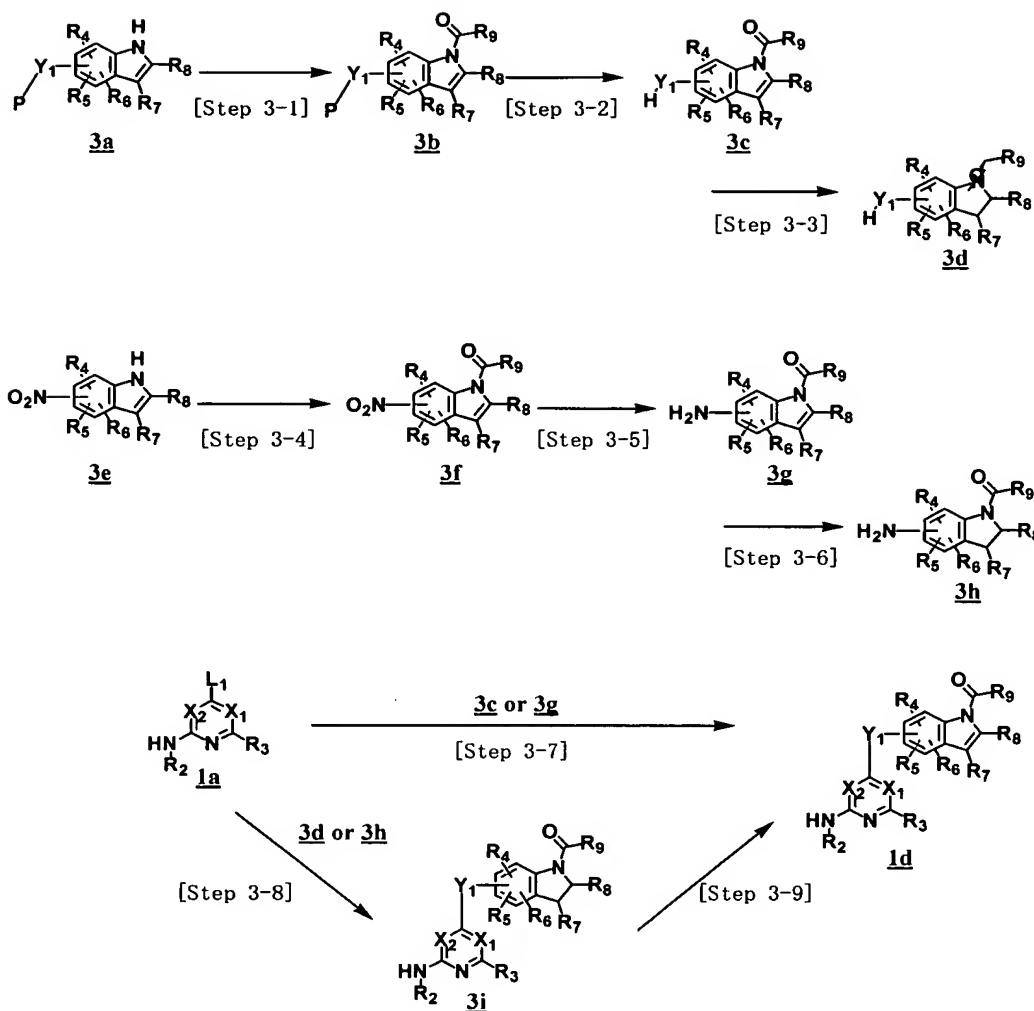
[0071]

[Production method 3]

Another production method of the compound (1d) via the compounds (3c), (3d), (3g) or (3h)

[0072]

[chemical formula 38]



[0073]

wherein, P represents a protecting group; other symbols represent the same definitions as in the aforementioned definitions.

<Step 3-1><Step 3-2><Step 3-3>

These are steps for obtaining an indole derivative (3c) or an indoline derivative (3d), both being introduced a carboxamide group at the 1-position, via a compound (3b) from an indole derivative (3a).

<Step 3-1> is a step for conducting carboxamidation of the 1-position of an indole derivative (3a) to obtain a compound (3b), and can be performed in a similar way as <Step 1A-2>. A methyl group, a benzyl group, a substituted benzyl group, a benzyloxycarbonyl group can be used as a protecting group, for example.

<Step 3-2> is a step for obtaining a compound (3c) by deprotecting an indole derivative (3b). Specifically, for example, in the case that Y₁ is an oxygen atom, the methods used for ordinal deprotection such as demethylation by using boron tribromide, debenzylation by using trifluoroacetic acid-thioanisole, debenzylation or the debenzyoxycarbonylation by catalytic reduction can be used.

<Step 3-3> is a step for reduction of an indole derivative (3c) to an indoline derivative (3d). Catalytic hydrogenation reaction in the presence of palladium catalyst under ordinal pressure or under pressurization or the like can be applied. Methanol, N,N-dimethylformamide, tetrahydrofuran or the like can be used as a reaction solvent, and the reaction can be performed for a time of 10 minutes to 30 hours at a temperature of 0 °C to reflux temperature. <Step 3-4><Step 3-5><Step 3-6>

These are steps for obtaining an aminoindole derivative (3g) or an aminoindoline derivative (3h) having a carboxamide group at the 1-position via a compound (3f) from a nitroindole derivative (3e).

<Step 3-4> is a step conducting carboxamidation of the 1-position of a indole derivative (3e) to obtain a compound (3f), and can be performed in the same way as in <Step 1A-2>.

5 <Step 3-5> is a step for reducing a nitroindole derivative (3f) to an aminoindole derivative (3g). The conditions used for reduction reaction of a nitro group to an aminogroup generally utilized, specifically, for example, reduction by iron-ammonium chloride or iron-acetic acid or
10 the like, catalytic reduction by palladium hydroxide-hydrogen or the like can be applied. Methanol, ethanol, water, N,N-dimethylformamide, tetrahydrofuran or the like can be used as a reaction solvent, and the reaction can be performed at a temperature of room temperature to
15 reflux temperature for 10 minutes to 30 hours.

<Step 3-6> is a step for reducing an indole derivative (3g) to an indoline derivative (3h) and can be performed in the same way as in <Step 3-3>.

<Step 3-7><Step 3-8>

20 These are steps for condensing an indole derivative (3c or 3g) or an indoline derivative (3d or 3h) and a compound (1a) to obtain an indole derivative (1d) or an indoline derivative (3h), and can be performed in the same way as in <Step 1A-1>.

25 <Step 3-9>

 This is a step for oxidizing an indoline derivative

(3h) to an indole derivative (1d). For example, 2,3-dichloro-5,6-diamino-1,4-benzoquinone (DDQ) or the like can be used as an oxidizing agent, and 1,4-dioxane, toluene, benzene or the like can be used as a solvent.

5 Alternatively, a method in which manganese acetate (III) is used as an oxidizing agent or the like as reported in Tetrahedron Lett. 29, 2151 (1988) can be applied.

In addition, in the case that Y_1 is the formula $-NR_Y-$ and R_Y is a hydrogen atom in compounds (3g), (3h), (3c) or
10 (3d), a compound (1d), wherein Y_1 is the formula $-NR_Y-$ and R_Y is a C_{1-6} alkyl group, can be also obtained by converting the hydrogen atom into a C_{1-6} alkyl group by a reductive amination reaction with aldehyde or ketone, and by using these for the respective following reactions. In addition,
15 in the case that Y_1 is the formula $-NR_Y-$ and R_Y is a hydrogen atom in compounds (3i) or (1d), the compounds can be also similarly converted into the compounds (3i) or (1d), wherein Y_1 is the formula $-NR_Y-$ and R_Y is a C_{1-6} alkyl group. In this case, sodium cyanoborohydride, sodium
20 trimethoxyborohydride or the like can be used as a reducing agent, and methanol, tetrahydrofuran, dichloromethane, dichloroethane or the like can be used as a reaction solvent. In addition, a method in which a benzotriazole derivative is prepared and is reduced by sodium borohydride as reported
25 in Tetrahedron 47, 2683 (1991) or the like can be applied.

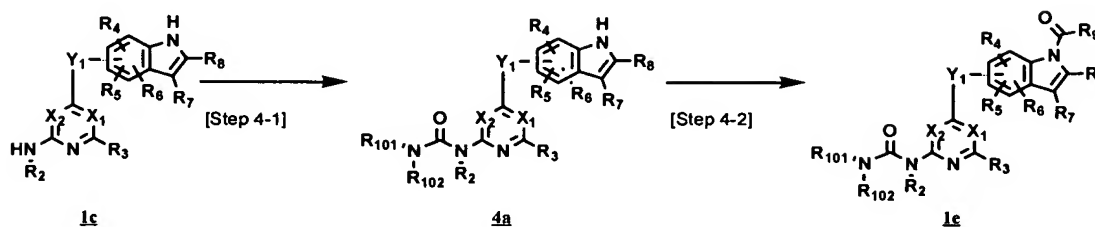
[0074]

[Production method 4]

Another production method of the compound (1e)

[0075]

[chemical formula 39]



[0076]

wherein each symbol represents the same definition as the
aforementioned definition.

<Step 4-1>

This is a step for converting a compound (1c) to a
compound (4a), and can be performed in the same way as in
<Step 1A-3>.

<Step 4-2>

This is a step for conducting carboxamidation of the
1-position of an indole derivative (4a) to obtain a compound
(1e), and can be performed in the same way as in <Step 1A-2>.

It is to be noted that, as described in [Production
method 1-A], a substituent conversion can be also performed
in R₂, R₉, R₁₀₁ and R₁₀₂ by properly performing oxidation
reaction, reduction reaction, reductive amination reaction,
ester formation reaction, amide formation reaction,
protecting group introduction reaction, deprotection

reaction, hydrolysis reaction or the like generally utilized after these steps.

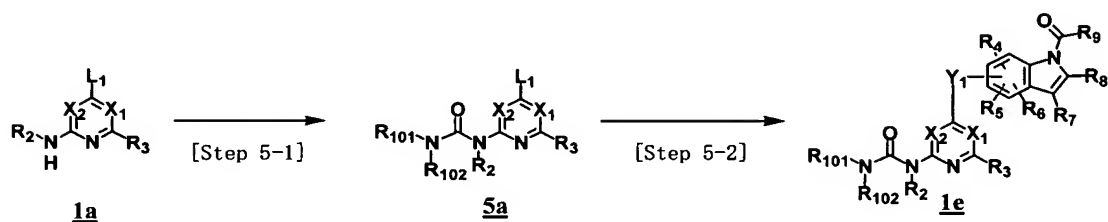
[0077]

[Production method 5]

5 Another production method of a compound (1e)

[0078]

[chemical formula 40]



10 [0079]

wherein, each symbol represents the same definition as the aforementioned definition.

<Step 5-1>

This is a step for converting a pyrimidine or pyridine derivative (1a) into a corresponding urea derivative (5a), and can be performed in the same way as in <Step 1A-3>.

<Step 5-2>

This is a step for obtaining a compound (1e) from a pyrimidine or pyridine derivative (5a) having urea. A method in which the same operations as in <Step 1A-1> and <Step 1A-2> are sequentially performed, a method in which the same operations as in <Step 2-1>, <Step 2-2> and <Step 1A-2> are sequentially performed, a method as in <Step 3-7>,

a method in which the same operations as in <Step 3-8> and
<Step 3-9> are sequentially performed or the like can be
applied.

It is to be noted that, as described in [Production
method 1-A], a substituent conversion can be also performed
in R₂, R₉, R₁₀₁ and R₁₀₂ by properly performing oxidation
reaction, reduction reaction, reductive amination reaction,
ester formation reaction, amide formation reaction,
protecting group introduction reaction, deprotection
reaction, hydrolysis reaction or the like generally utilized
after these steps.

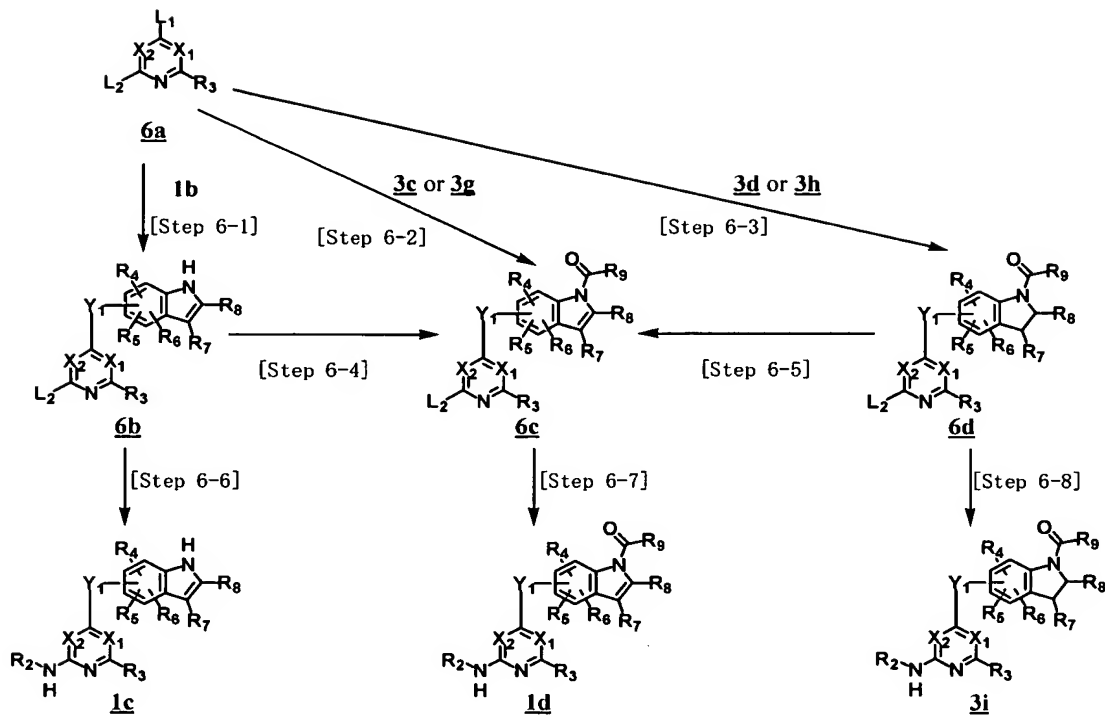
[0080]

[Production method 6]

Another manufacturing method of compounds (1c), (1d), (3i)

[0081]

[chemical formula 41]



[0082]

wherein, L_2 represents a leaving group; each symbol
 5 represents the same definition as the aforementioned
 definition.

<Step 6-1><Step 6-2><Step 6-3>

These are steps for condensing a pyrimidine or pyridine
 derivative having leaving groups L_1 and L_2 and an indole
 10 or indoline derivative. In these steps, it is preferable
 that L_1 is a substituent having higher reactivity than that
 of L_2 . Specifically, for example, a combination of L_1 being
 a nitro group and L_2 being a chlorine atom or the like comes
 under the category. By using an indole derivative (**1b**),
 15 indole derivatives (**3c**), (**3g**) having a carboxamide group

at the 1-position, indoline derivatives (3d), (3h) having a carboxamide group at the 1-position, each compound (6b), (6c) and (6d) can be obtained under the same conditions as in <Step 1A-1>.

5 <Step 6-4>

This is a step for conducting carboxamidation of the 1-position of indole in a compound (6b) to obtain a compound (6c), and can be performed in the same way as in <Step 1A-2>.

<Step 6-5>

10 This is a step for oxidizing an indoline derivative (6d) to an indole derivative (6c). The same method as in <Step 3-9> can be used.

<Step 6-6><Step 6-7><Step 6-8>

15 These are steps in which the leaving group L_2 of pyrimidine or pyridine derivatives (6b), (6c), or (6d) is converted into a group represented by the formula $-NHR_2$, wherein R_2 represents the same definition as the aforementioned definition, to obtain compounds (1c), (1d), or (3i), respectively. For example, an ammonia-ethanol solution or a corresponding primary amine is used, and the reaction can be performed in a sealed tube for a time of 10 minutes to 100 hours at a temperature of 60 ° C to reflux temperature.

[0083]

25 [Production method 7]

Another production method of a compound (7j), which is the

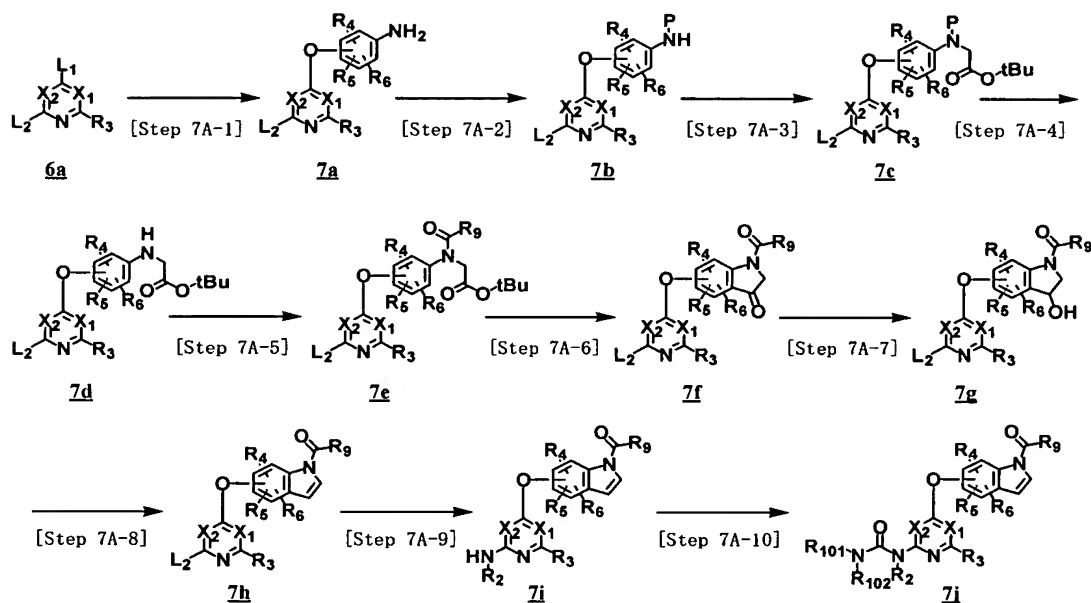
compound represented by the formula (Ia), wherein Y is an oxygen atom and both 2- and 3-positions of indole (R_8 , R_7) are hydrogen atoms

[production method 7-A]

5

[0084]

[chemical formula 42]



[0085]

wherein each symbol represents the same definition as the aforementioned definition.

10

<Step 7A-1>

This is a step for obtaining a compound (7a) by introducing an aminophenoxy group into a compound (6a). It is preferable that in the compound (6a), L_1 is a substituent having higher reactivity than that of L_2 . Specifically, for example, a combination of L_1 being a nitro group and L_2 being a chlorine atom comes under the category. A compound

15

(7a) can be obtained by using a compound (6a) and an aminophenol derivative in the same method as in <Step 1A-1>. In addition, after these compounds are condensed by using a nitrophenol derivative in the same way as in <Step 1A-1>, a method for reducing a nitro group by catalytic hydrogenation reaction using palladium catalyst or the like, or metal reduction reaction using iron-ammonium chloride, iron-acetic acid or the like can be applied. In the reduction reaction of the nitro group, methanol, ethanol, tetrahydrofuran, N,N-dimethylformamide or the like can be used as a reaction solvent, and the catalytic hydrogenation reaction can be performed at ordinary pressure or under pressurization. The reaction can be performed at a temperature of room temperature to reflux temperature for 10 minutes to 30 hours.

<Step 7A-2>

This is a step for protecting amino group of a compound (7a) to obtain a compound (7b). As a protecting group, for example, a benzyloxycarbonyl group or the like can be introduced by using a corresponding chlorocarbonate ester.

<Step 7A-3>

This is a method for obtaining a compound (7c) from a compound (7b). t-Butyl bromoacetate ester as a reagent, sodium hydroxide or the like as a base, N,N-dimethylformamide, tetrahydrofuran, dimethyl sulfoxide or the like as a reaction solvent can be used. The reaction can be performed at a

temperature of room temperature to reflux temperature for 10 minutes to 30 hours.

<Step 7A-4>

5 This is a step for deprotecting a compound (7c) to obtain a compound (7d). There may be mentioned, for example, deprotection reaction by the catalytic hydrogenation reaction of benzyloxycarbonyl group or the like.

<Step 7A-5>

10 This is a step for obtaining a compound (7e) by introducing a carboxamide group to a compound (7d). As a reagent, an isocyanate derivative, a carbamate derivative or the like can be used. As a reaction solvent, N,N-dimethylformamide, tetrahydrofuran, dimethyl sulfoxide, toluene or the like can be used, and organic bases
15 such as triethylamine or pyridine can be added thereto as requested. The reaction can be performed for a time of 10 minutes to 30 hours and at a temperature of 0 ° C to reflux temperature.

<Step 7A-6>

20 This is a step for obtaining a compound (7f) from a compound (7e) by cyclization reaction. The reaction is performed in an acidic condition, specifically, for example, in trifluoroacetic acid-trifluoroacetic anhydride or the like. The reaction can be performed for a time of 10 minutes
25 to 30 hours and at a temperature of 0 ° C to reflux temperature.

<Step 7A-7><Step 7A-8>

These are steps for converting into an indole derivative (7h) via a compound (7g) from a 3-oxoindoline derivative (7f). A 3-hydroxyindoline derivative (7g) is prepared by reduction of a carbonyl group using sodium borohydride as a reagent, in tetrahydrofuran, methanol, ethanol or the like as a reaction solvent, thereafter a compound (7h) can be obtained by performing dehydration by using camphor sulfonic acid or the like as a reagent, and toluene, dichloroethane or the like as a reaction solvent.

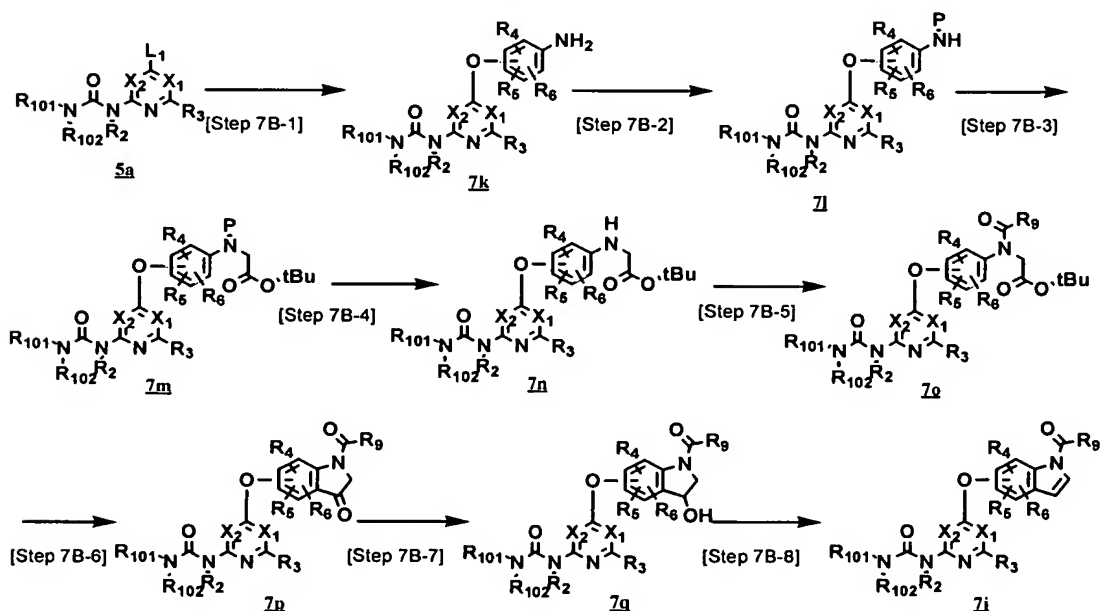
<Step 7A-9><Step 7A-10>

Thereafter, it is possible to lead to a step in which a compound (7j) is prepared under the same conditions in each of <Step 6-6>, <Step 1A-3>

[Production method 7-B]

[0086]

[chemical formula 43]



[0087]

wherein, each symbol represents the same definition as the
aforementioned definition.

5 <Step 7B-1>

This is a step for obtaining a compound (7k) from a
compound (5a), and can be performed in the same way as in
<Step 7A-1>.

<Step 7B-2>

10 This is a step for protecting an amino group of a
compound (7k) to obtain a compound (7l), and can be performed
in the same way as in <Step 7A-2>.

<Step 7B-3>

15 This is a method for obtaining a compound (7m) from
a compound (7l), and can be performed in the same way as
in <Step 7A-3>.

<Step 7B-4>

20 This is a step for deprotecting a compound (7m) to
obtain a compound (7n), and can be performed in the same
way as in <Step 7A-4>.

<Step 7B-5>

This is a step for introducing a carboxamide group
to a compound (7n) to obtain a compound (7o), and can be
performed in the same way as in <Step 7A-5>.

25 <Step 7B-6>

This is a step for obtaining a cyclized compound (7p)

from a compound (7o), and can be performed in the same way as in <Step 7A-6>.

<Step 7B-7><Step 7B-8>

These are steps for converting into an indole derivative (7j) via a compound (7q) from a 3-oxoindoline derivative (7p), and can be performed in the same as in <Step 7A-7><Step 7A-8>.

[0088]

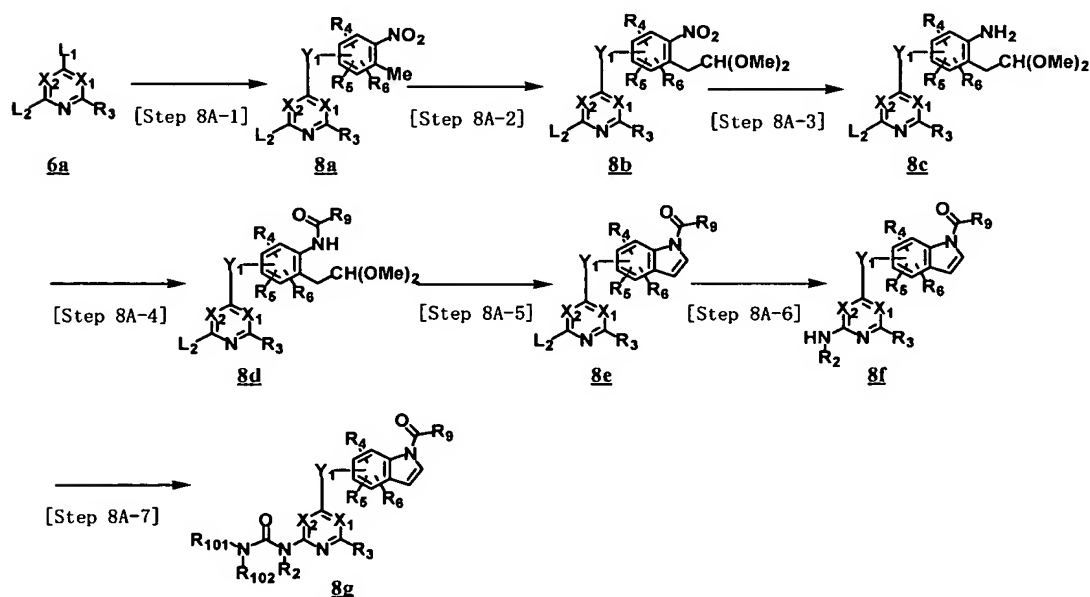
[Production process 8]

Another production method of a compound (8g), which is the compound represented by the formula (Ia), wherein both 2- and 3-positions of indole (R_8, R_7) are hydrogen atoms

[Production method 8-A]

[0089]

[chemical formula 44]



[0090]

wherein, each symbol represents the same definition as the
aforementioned definition.

<Step 8A-1>

5 This is a coupling reaction of a compound (6a) with
a nitrobenzene derivative. A compound (8a) can be obtained
under the same conditions as in <Step 1A-1>.

<Step 8A-2>

10 This is a step for obtaining a compound (8b) from a
compound (8a). The reaction can be performed under the
conditions as described in Tetrahedron Lett. 39, 71 (1998).
Specifically, a dimethylacetal compound can be derived by
condensing a nitrotoluene derivative and dimethylformamide
dimethylacetal in N,N-dimethylformamide at a temperature
of room temperature to reflux temperature for 10 minutes
15 to 30 hours, and by sequentially performing the reaction
of the compound in methanol under acidic condition at a
temperature of room temperature to reflux temperature for
10 minutes to 30 hours.

<Step 8A-3>

20 This is a step for reducing a compound (8b) to a compound
(8c). Reduction by iron-ammonium chloride, iron-acetic
acid or the like can be used. As a reaction solvent, methanol,
ethanol, tetrahydrofuran, N,N-dimethylformamide or the
like can be used. The reaction can be performed at a
25 temperature of room temperature to reflux temperature for
10 minutes to 30 hours.

<Step 8A-4>

This is a step for converting a compound (8c) into a urea derivative to obtain a compound (8d), and can be performed in the same way as in <Step 7A-5>. Alternatively, tetrahydrofuran or N,N-dimethylformamide is used as a reaction solvent, for example, after a carbamate derivative is prepared by using phenyl chlorocarbonate or the like, and urea can be also introduced by allowing the derivative to react with an amine at a temperature of room temperature to reflux temperature for 10 minutes to 30 hours, while N,N-dimethylformamide, dimethyl sulfoxide are used as a reaction solvent.

<Step 8A-5>

This is a step for cyclizing a compound (8d) to obtain a compound (8e). The reaction can be performed under the conditions as described in Tetrahedron Lett. 39, 71 (1998). Specifically, there may be mentioned a method in which reflux is performed in solvents such as benzene in the presence of catalytic amounts of camphor sulfonic acid and quinoline.

<Step 8A-6>

This is a step for obtaining a compound (8f) from a compound (8e), and can be performed in the same way as in <Step 6-6>.

<Step 8A-7>

This is a step for obtaining a compound (8g) from a compound (8f), and can be performed in the same way as in

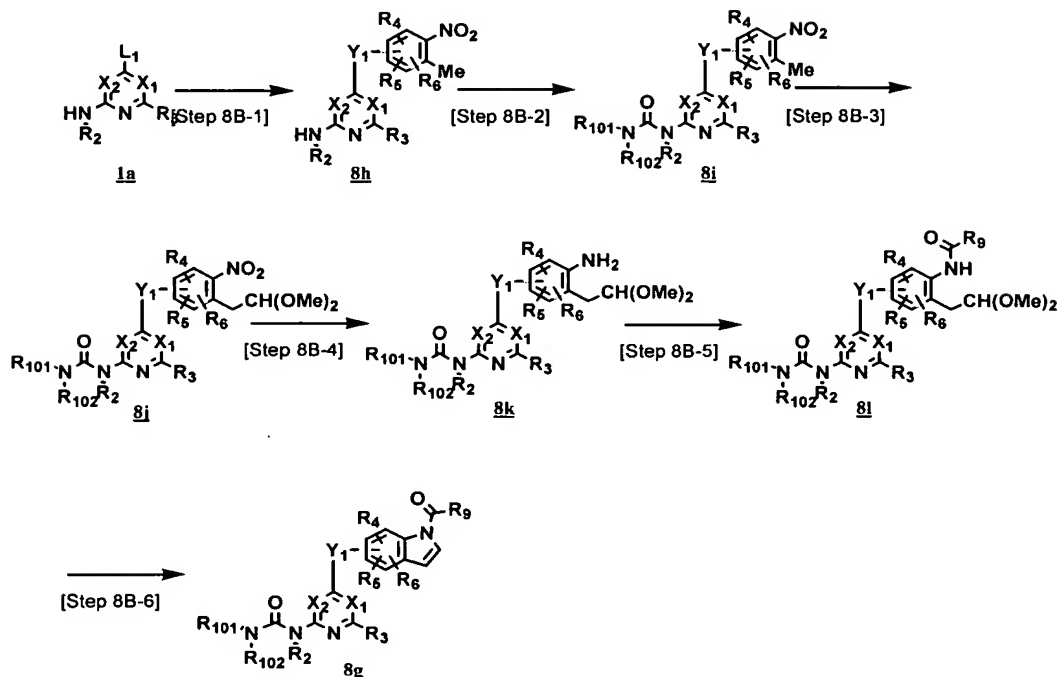
<Step 7A-10>.

[0091]

[Production method 8-B]

[0092]

5 [chemical formula 45]



[0092]

wherein, each symbol represents the same definition as in the aforementioned definition.

10 <Step 8B-1>

This is a step for obtaining a compound (8h) by performing coupling reaction of a compound (1a) with a nitrobenzene derivative, and can be performed in the same way as in <Step 1A-1>.

15 <Step 8B-2>

This is a step for introducing urea to a compound (8h)

to obtain a compound (8i), and can be performed in the same way as in <Step 1A-3>.

<Step 8B-3>

This is a step for condensing a nitrotoluene derivative (8i) and dimethylformamide dimethylacetal, subsequently, for deriving the compound to dimethylacetal compound (8j). The step can be performed in the same way as in <Step 8A-2>.

<Step 8B-4>

This is a step for reducing a nitro group of a compound (8j) to obtain a compound (8k), and can be performed in the same way as in <Step 8A-3>.

<Step 8B-5>

This is a step for obtaining a compound (8l) from a compound (8k) by introducing urea, and can be performed in the same way as in <Step 8A-4>.

<Step 8B-6>

This is a step for cyclizing a compound (8l) to obtain a compound (8g), and can be performed in the same way as in <Step 8A-5>.

[0094]

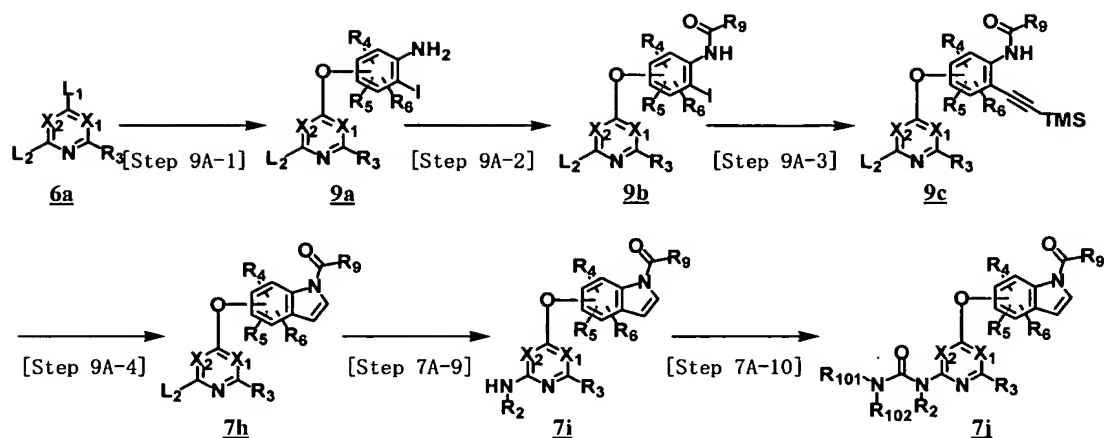
[Production method 9]

Another production method of a compound (7j)

[Production method 9-A]

[0095]

[chemical formula 46]



[0096]

wherein, each symbol represents the same definition as the
 5 aforementioned definition.

<Step 9A-1>

This is a step for obtaining a compound (9a) by coupling
 of a compound (6a) with a phenol derivative. Specifically,
 for example, a corresponding condensed compound can be
 10 obtained under the same conditions as in <Step 1A-1>, by
 using 4-amino-3-iodophenol obtained from t-butyl
 (2-iodo-4-((triisopropylsilyl)oxy)phenyl)carbamate
 obtained by a method as described in J. Org. chem., 62, 6507
 (1997) by allowing n-butylammonium fluoride or the like to
 15 react therewith.

<Step 9A-2>

This is a step for converting a compound (9a) into
 a urea derivative to obtain a compound (9b), and can be
 performed in the same way as in <Step 8A-4>.

<Step 9A-3>

This is a step for obtaining an acetylene derivative (9c) from an iodo compound (9c) using trimethylsilylacetylene. The condensation can be performed in the presence of tetrakis(triphenylphosphine)palladium or dichlorobis(triphenylphosphine)palladium, cuprous iodide. N,N-dimethylformamide or the like can be used as a reaction solvent, and the reaction can be performed at a temperature of room temperature to reflux temperature for 10 minutes to 30 hours.

<Step 9A-4>

This is a step for performing cyclization by heating an acetylene derivative (9c) in the presence of cuprous iodide to obtain an indole derivative (7h). N,N-dimethylformamide or the like can be used as a reaction solvent, and the reaction can be performed at a temperature of 80 ° C to reflux temperature for 5 minutes to 10 hours.

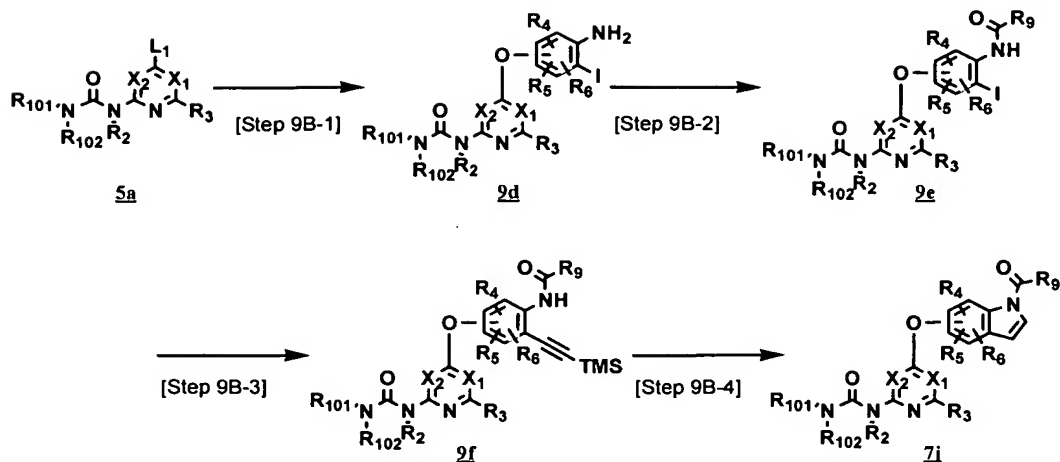
Subsequently, a compound (7h) can be converted into a compound (7j) as described in <Step 7A-9>, <Step 7A-10>.

[0097]

[Production method 9-B]

[0098]

[chemical formula 47]



[0099]

wherein each symbol represents the same definition as in the aforementioned definition.

5 <Step 9B-1>

This is a step for coupling a compound (5a) with a phenol derivative to obtain a compound (9d), and can be performed in the same way as in <Step 9A-1>.

<Step 9B-2>

10 This is a step for converting a compound (9d) into a urea derivative to obtain a compound (9e), and can be performed in the same way as in <Step 7A-5>.

<Step 9B-3>

15 This is a step for obtaining an acetylene derivative (9f) from an iodo compound (9e) by using trimethylsilylacetylene, and can be performed in the same way as in <Step 9A-3>.

<Step 9B-4>

This is a step for cyclizing an acetylene derivative

(9f) by heating in the presence of cuprous iodide to obtain an indole derivative (7j). The same conditions as in <Step 9A-4> can be applied.

[0100]

5 After completing the aforementioned reactions, purification can be performed by a ordinal treatment method, for example, column chromatography using silica gel or adsorbent resins or the like, or recrystallization from a suitable solvent.

10 [0101]

 The compounds of the invention, salts thereof or hydrates of the foregoing may be formulated as tablets, powders, fine particles, granules, coated tablets, capsules, syrups, lozenges, inhalants, suppositories, injections, 15 ointments, eye salves, eye drops, nasal drops, ear drops, paps, lotions and the like, by any common methods. The formulation may employ any commonly used excipients, binders, lubricants, coloring agents, corrective coatings, and if necessary, stabilizers, emulsifiers, absorbefacients, 20 surfactants, pH adjustors, preservatives, antioxidants, or the like, in combination with various components that are ordinarily used as raw materials for pharmaceutical formulations. For example, an oral formulation may be prepared by combining a compound of the invention or 25 pharmacologically acceptable salt thereof with an excipient, if necessary adding a binder, disintegrator, lubricant,

coloring agent, corrective coating or the like, and forming
a powder, fine particles, granules, tablets, coated tablets,
capsules, etc. by a common method. As such components there
may be mentioned animal and vegetable oils such as soybean
oil, beef tallow and synthetic glycerides; hydrocarbons such
as liquid paraffin, squalane and solid paraffin; ester oils
such as octyldodecyl myristate and isopropyl myristate;
higher alcohols such as cetostearyl alcohol and behenyl
alcohol; silicone resins; silicone oils; surfactants such
as polyoxyethylene fatty acid esters, sorbitan fatty acid
esters, glycerin fatty acid esters, polyoxyethylene
sorbitan fatty acid esters, polyoxyethylene hydrogenated
castor oil and polyoxyethylene-polyoxypropylene block
copolymer; water-soluble polymers such as
hydroxyethylcellulose, polyacrylic acid, carboxyvinyl
polymer, polyethylene glycol, polyvinylpyrrolidone and
methylcellulose; lower alcohols such as ethanol and
isopropanol; polyhydric alcohols such as glycerin,
propylene glycol, dipropylene glycol and sorbitol; sugars
such as glucose and sucrose; inorganic powders such as
silicic acid anhydride, magnesium aluminum silicate and
aluminum silicate, purified water, and the like. Examples
of excipients which may be used include lactose, corn starch,
white soft sugar, glucose, mannitol, sorbit, crystalline
cellulose and silicon dioxide, examples of binders which
may be used include polyvinyl alcohol, polyvinyl ether,

methycellulose, ethylcellulose, gum arabic, tragacanth,
gelatin, shellac, hydroxypropylmethycellulose,
hydroxypropylcellulose, polyvinylpyrrolidone,
polypropylene glycol/polyoxyethylene block polymer and
5 meglumine, examples of disintegrators which may be used
include starch, agar, gelatin powder, crystalline cellulose,
calcium carbonate, sodium bicarbonate, calcium citrate,
dextrin, pectin and carboxymethylcellulose calcium,
examples of lubricants which may be used include magnesium
10 stearate, talc, polyethylene glycol, silica and
hydrogenated vegetable oils, examples of coloring agents
which may be used include those approved for addition to
drugs, and examples of corrective coatings which may be used
include cocoa powder, menthol, aromatic powders, mentha oil,
15 borneol and powdered cinnamon. The tablets or granules may
also be sugar coated or provided with another type of suitable
coating if necessary. For preparation of a liquid
formulation such as a syrup or injection, a common method
may be used to formulate a compound of the invention or a
20 pharmacologically acceptable salt thereof with a pH adjustor,
solubilizer, isotonizing agent or the like, as well as a
solubilizing aid, stabilizer etc. if necessary. There are
no particular restrictions on the method of preparing an
external agent, and any common method may be employed. That
25 is, it may be prepared using as base materials any of various
raw materials which are ordinarily used in drugs, quasi drugs,

cosmetics and the like. As examples of specific base materials there may be mentioned raw materials such as animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals, purified water and the like, and if necessary pH adjustors, antioxidants, chelating agents, antiseptics and fungicides, coloring agents, aromas and the like may also be added, although the base materials for external agents according to the invention are not limited to these. If necessary, there may also be included components such as ingredients having differentiation-inducing activity, circulation promoters, microbicides, antiphlogistic agents, cell activators, vitamins, amino acids, humectants, keratolytic agents and the like. The amounts of the aforementioned base materials may be the concentrations established for preparation of ordinary external agents.

[0102]

There are no particular restrictions on the compound of the invention, the salt thereof or the hydrate thereof when administered, and either oral or parenteral administration may be carried out according to ordinary methods. For example, it may be prepared and administered in the form of a tablet, powder, a granule, a capsule, syrup, lozenge, inhalant, suppository, injection, ointment, eye

salve, eye drop, nasal drop, ear drop, pap, lotion or the like.

[0103]

Although the dosage of a drug according to the invention will differ depending on severity of symptoms, age, gender, body weight, form of administration, type of disease, etc., it will be generally 100 µg - 10 g per day for an adult and such dosages may be administered once or divided over several.

The administration form of the medicine according to the present invention is not particularly restricted, and can be an oral administration or a parenteral administration by a generally employed method.

[0104]

The biochemical activity and actions and effects (angiogenesis inhibition activity, antitumor activity or the like) as a medicine of the compounds according to the present invention can be evaluated by the following methods.

The following is a list of abbreviations used in the pharmacological test examples described below.

<List of Abbreviations>

DNA (deoxyribonucleic acid)

VEGFR2 (vascular endothelial growth factor receptor 2)

human placenta (human placenta)

Hepes

(N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic

acid], HEPES (buffer solution))

MgCl₂ (Magnesium Chloride)

MnCl₂ (Manganese Chloride)

Na₃VO₄ (Sodium Orthovanadate(V))

5 ATP (Adenosine 5'-Triphosphate)

EDTA (Ethylenediaminetetraacetic acid)

HTRF (Homogenous Time-Resolved Fluorescence)

FGFR1 (Fibroblast growth factor receptor 1)

PDGFRβ (Platelet derived growth factor receptor β)

10 HGFR (Hepatocyte growth factor receptor)

EGFR (Epidermal growth factor receptor)

Tris (Tris (hydroxymethyl)aminomethane, tris (buffer solution))

NaCl (sodium Chloride)

15 BSA (Bovine Serum Albumin)

HRP (Horseradish peroxidase)

EGTA (N,N,N',N'-tetraacetic acid)

SDS (Sodium Dodecylsulphate)

NP-40 (Nonidet P-40)

20 PCR: polymerase chain reaction

RT-PCR: reverse transcription-polymerase chain reaction

RNA: ribonucleic acid

cDNA: complementary DNA

cRNA: complementary RNA

25 dNTP: a mixture composed of dATP, dCTP, dGTP and dTTP

UTP: Uridine 5'-triphosphate

CTP: Cytidine 5'-triphosphate

dATP: 2'-Deoxyadenosine 5'-triphosphate

dCTP: 2'-Deoxycytidine 5'-triphosphate

dGTP: 2'-Deoxyguanosine 5'-triphosphate

5 dUTP: 2'-Deoxyuridine 5'-triphosphate

GAPDH: glyceraldehydes 3-phosphate dehydrogenase

FBS: Fetal bovine serum

PBS: Phosphate buffered saline

MTT:

10 (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium
bromide; Thiazolyl blue)

DMSO: Dimethyl sulfoxide

PDGF: Platelet derived growth factor

EGF: Epidermal growth factor

15 FGF2: Fibroblast growth factor 2

VEGF: Vascular endothelial growth factor

HGF: Hepatocyte growth factor

TNF- α : Tumor Necrosis factor alpha

FCS: Fetal Bovine Serum

20 EGM-2: Endothelial Cell Growth Medium-2

[0105]

Pharmacological Test Example 1: Inhibition against sandwich
tube formation by vascular endothelial cells in response
to stimulation by angiogenesis factor

25 Human Umbilical Vein Endothelial Cells (HUVECs) were
isolated according to a reported method (Shinseikagaku

Jikken Koza [New Biochemistry Experiment Lectures], "Saibo Baiyo Gijutsu" [Cell Culturing Techniques], p.197-202), and were cultured in a 5% CO₂ incubator (37°C) using EGM-2 medium (purchased from Clonetics Corp.) until the cells reached confluency.

An ice-cooled mixture of collagen: 5x RPMI 1640: reconstitution buffer (all purchased from Nitta Gelatin, Inc.) at 7:2:1 was dispensed at 0.4 ml into each well of a 24-well plate. After the solution was gelled by being stationed for 40 minutes in a 5% CO₂ incubator (37°C), HUVEC cell suspension was added at 0.4 ml to each well (using 1 to 1.2 x 10⁵ cells, though the numbers of cells differs slightly according to the HUVEC lot), the HUVEC cell suspension being in human endothelial serum free medium (SFM, purchased from GIBCO BRL) containing added angiogenesis factors [20 ng/ml FGF2 (purchased from GIBCO BRL) and 10 ng/ml EGF (purchased from GIBCO BRL), or 25 ng/ml VEGF (purchased from Wako Pure Chemical Industries Co., Ltd.) and 10 ng/ml EGF, or 30 ng/ml HGF (purchased from R&D Co.) and 10 ng/ml EGF], and cultured overnight in a 5% CO₂ incubator (37°C). On the following day, the medium on the upper layer was aspirated off, and then 0.4 ml of an ice-cooled mixture of collagen: 5x RPMI 1640: reconstitution buffer (all purchased from Nitta Gelatin, Inc.) at 7:2:1 was superposed into each well prior to stationing for 4 hours in a 5% CO₂ incubator (37°C) for gelling. After adding 1.5 ml of an SFM solution containing

each of the aforementioned angiogenesis factors and a diluted test substance onto the upper layer, culturing was performed in a 5% CO₂ incubator (37°C). Upon aspirating off the culture supernatant in each well on the 4th day after addition of the test substance, 0.4 ml of a 3.3 mg/ml MTT solution dissolved in PBS (purchased from Sigma Corp.) was added to each well and culturing was performed for approximately 2 hours in a 5% CO₂ incubator (37°C). The tubes formed in the collagen gel of each well were stained by MTT, the tube images were loaded into a computer (Macintosh), and the total length of the tubes was determined by image analysis software "MacScope" (purchased from Mitani Corp.). The ratio of the total length of the tubes formed in the well containing the test substance with respect to the total length of the tubes formed in the well containing no test substance was expressed as a percentage, and the concentration of each test substance required for 50% inhibition of tube formation (IC₅₀) was determined from the ratio value. The results are shown in Table 1.

[0106]

[Table 1]

Example No.	VEGF-stimulated tube formation IC ₅₀ (nM)	FGF2-stimulated tube formation IC ₅₀ (nM)
39	5.1	470
41	2.1	250
46	7.0	470
47	5.8	120
53	6.7	440

[0107]

Pharmacological Test Example 2: Measurement of inhibition
against receptor tyrosine kinase activity

5 This assay is used to determine inhibition of a test
substance on tyrosine kinase activity. DNA coding for the
cytoplasmic domain of VEGFR2 is obtained by total cDNA
synthesis (Edwards M, International Biotechnology Lab 5(3),
19-25, 1987) or by cloning. Expression in an appropriate
expression system can produce a polypeptide with tyrosine
10 kinase activity. The cytoplasmic domain of VEGFR2 obtained
by expression of recombinant protein in, for example, insect
cells have been found to exhibit intrinsic tyrosine kinase
activity. For VEGFR2 (GenBank Accession No. L04947), the
1.7 kb DNA fragment described by Terman et al. (Oncogene,
15 6(9), 1677-1683, 1991), coding for the cytoplasmic domain,
beginning with lysine 791 and including the termination codon,
was isolated from a human placental cDNA library (purchased
from Clontech Laboratories, Inc.) and cloned in a Baculovirus
transplace vector (pBlueBacHis, purchased from GIBCO BRL).
20 The recombinant construct was transfected into insect cells
(*Spondoptea frugiperda* 9 (Sf9)) to prepare a recombinant
Baculovirus. (Instructions for preparation and use of
recombinant Baculovirus may be found in standard texts, such
as "Bac-To-Bac Baculovirus Expression System" (GIBCO BRL).)
25 The cytoplasmic fragment starting from lysine 398 (FGFR1,
GenBank Accession No. X52833), the cytoplasmic fragment

starting from lysine 558 (PDGFR β , GenBank Accession No. M21616) or the cytoplasmic fragment starting from lysine 974 (HGFR, GenBank Accession No. J02958) may be cloned and expressed by the same method for use in assays for other tyrosine kinases. EGFR was purchased from Sigma Co. (Product No. E-2645).

For expression of the VEGFR2 tyrosine kinase, Sf9 cells were infected with the VEGFR2 recombinant virus and collected after 48 hours. The collected cells were rinsed with ice-cooled phosphate buffered saline (PBS) and then resuspended using 20 ml of ice-cooled Lysis Buffer (50 mM Tris-HCl (pH 8.5), 5 mM 2-mercaptoethanol, 100 mM KCl, 1 mM phenylmethylsulfonyl fluoride, 1% (v/v) NP-40) per 1.5×10^8 cells. The suspension was centrifuged at 12,000 rpm for 30 minutes at 4°C and the supernatant was obtained. The supernatant was added to a Ni-NTA agarose column (3 ml, purchased from Qiagen) equilibrated with Buffer A {20 mM Tris-HCl (pH 8.5), 5 mM 2-mercaptoethanol, 500 mM KCl, 20 mM imidazole, 10% (v/v) glycerol}. The column was washed with 30 ml of Buffer A, and then with 6 ml of Buffer B {20 mM Tris-HCl (pH 8.5), 5 mM 2-mercaptoethanol, 1M KCl, 10% (v/v) glycerol}, and finally with 6 ml of Buffer A. After washing, it was eluted with 6 ml of Buffer C {20 mM Tris-HCl (pH 8.5), 5 mM 2-mercaptoethanol, 100 mM KCl, 100 mM imidazole, 10% (v/v) glycerol}. The eluate was placed on a dialysis membrane (purchased from Spectrum Laboratories) and

dialyzed with a dialysis buffer {20 mM Tris-HCl (pH 7.5), 10% (v/v) glycerol, 1 mM dithiothreitol, 0.1 mM Na_3VO_4 , 0.1 mM EGTA}. After dialysis, it was supplied for SDS-electrophoresis, and the recombinant protein (His6-VEGFR2, cytoplasmic domain of VEGFR2 fused with 6 histidine residues at the N-terminus) detected at a molecular weight of approximately 100 kDa with Coomassie Brilliant Blue staining was assayed using BSA (bovine serum albumin, purchased from Sigma Co.) as the standard substance, and stored at -80°C until use. Using the same method for the cytoplasmic domains of FGFR1, PDGFR β and HGFR yielded respective recombinant proteins fused with 6 histidine residues at the N-termini (His6-FGFR1, His6-PDGFR β or His6-HGFR).

The tyrosine kinase reaction was conducted as follows. In the case of VEGFR2, for example, 10 μl of a kinase reaction solution {200 mM Hepes (pH 7.4), 80 mM MgCl_2 , 16 mM MnCl_2 , 2 mM Na_3VO_4 }, 250 ng of biotin-bound poly(Glu4:Tyr1) (biotin-poly(GT), purchased from CIS Diagnostics Co.) (6 μl of a 15-fold dilution with distilled water), 15 ng of His6-VEGFR2 (10 μl of a 240-fold dilution with 0.4% BSA solution) and the test substance dissolved in dimethylsulfoxide (4 μl of a 100-fold dilution with 0.1% BSA solution) were added into each well of a 96-well round-bottom plate (NUNC Co., Product No. 163320), to a total of 30 μl . Next, 10 μl of 4 μM ATP (diluted with distilled

water) was added prior to incubation at 30°C for 10 minutes, and then 10 µl of 500 mM EDTA (pH 8.0) was added. The tyrosine-phosphorylated biotin-poly(GT) was measured by the Homogenous Time-Resolved Fluorescence (HTRF) method (Analytical Biochemistry, 269, 94-104, 1999). Specifically, the kinase reaction solution was transferred to a 96-well black half-plate (Product No. 3694, Coster, Inc.), 7.5 ng of europium cryptate-labeled anti-phosphotyrosine antibody (Eu(K)-PY20, purchased from CIS Diagnostics Co.) (25 µl of a 250-fold dilution with 20 mM Hepes (pH 7.0), 0.5 M KF, 0.1% BSA solution) and 250 ng of XL665-labeled streptavidin (XL665-SA, purchased from CIS Diagnostics Co.) (25 µl of a 62.5-fold dilution with 20 mM Hepes (pH 7.0), 0.5 M KF and 0.1% BSA solution) were added thereto, the mixture was allowed to stand at room temperature for 30 minutes, and then the fluorescent intensity was measured at 665 nm and 620 nm under irradiation with an excitation wavelength of 337 nm using a Discovery HTRF Microplate Analyzer (Packard Co.). The tyrosine phosphorylation rate for the biotin-poly(GT) was expressed as the delta F% value as described in the HTRF Standard Experiment Methods text by CIS Diagnostics Co. The delta F% value in the presence of the test substance was determined as a ratio (%) with the delta F% value with addition of His6-VEGFR2 in the absence of the test substance defined as 100% and the delta F% value in the absence of both the

test substance and His6-VEGFR2 defined as 0%. This ratio (%) was used to calculate the test substance concentration required for 50% inhibition of VEGFR2 kinase activity (IC_{50}).

Measurement of inhibition against FGFR1, EGFR and HGFR kinase activity was conducted using 15 ng of His6-FGFR1, 23 ng of EGFR and 30 ng of His6-HGFR, respectively, according to the tyrosine kinase reaction and HTRF method described above. Measurement of inhibition against PDGFR β kinase activity was conducted using 50 ng of His6-PDGFR β according to the tyrosine kinase reaction described above, followed by detection of tyrosine phosphorylated biotin-poly(GT) by the following method. Specifically, the kinase reaction solution was added to a 96-well streptavidin-coated plate (Product No. 15129, Pierce Chemical) and incubated at room temperature for 30 minutes. After rinsing 3 times with 150 μ l of a rinsing solution {20 mM Tris-HCl (pH 7.6), 137 mM NaCl, 0.05% Tween-20, 0.1% BSA}, 70 μ l of anti-phosphotyrosine (PY20)-HRP conjugate (Product No. P-11625, Transduction Laboratories) {2000-fold dilution with 20 mM Tris-HCl (pH 7.6), 137 mM NaCl, 0.05% Tween-20, 1% BSA} was added thereto and incubation was performed at room temperature for 1 hour. After incubation, it was rinsed 3 times with 150 μ l of the rinsing solution, and 100 μ l of TMB Membrane Peroxidase Substrate (Product No. 50-5077-03, Funakoshi Co., Ltd.) was added to initiate the reaction. After stationing at room temperature for 10 minutes, 100

5 μ l of 1 M phosphoric acid was added to suspend the reaction,
 and the absorbance at 450 nm was measured with a microplate
 reader (BIO KINETICS READER EL304, Bio-Tek Instruments).
 The absorbance ratio in the presence of the test substance
 was determined with respect to 100% as the absorbance with
 addition of His6-PDGFR β and no test substance, and 0% as
 the absorbance without addition of the test substance or
 His6-PDGFR β . This absorbance ratio was used to calculate
 the test substance concentration required for 50% inhibition
 10 of PDGFR β kinase activity (IC₅₀). The results are shown in
 Table 2.

[0108]

[Table 2]

Example No.	VEGFR2 kinase IC ₅₀ (nM)	FGFR1 kinase IC ₅₀ (nM)
28	4.5	4.1
36	3.4	16
37	4.8	1.2
39	4.5	6.3
41	6.1	3.2
46	32	12
47	40	21
50	5.0	13
53	3.8	2.1

[0109]

15 Pharmacological Test Example 3: Evaluation of *in vivo*
angiogenesis-inducing activity using mouse dorsal air sac
model

[1] Construction of VEGF (Vascular Endothelial Growth
 Factor) expression vector

PCR was conducted using a human placenta cDNA library (Toyobo Co., Ltd.) as the template and the SEQ ID NO:1 (5'CCGGATCCATGAACTTTCTGCTG3') and SEQ ID NO:2 (5'GTGAATTCTGTATCGATCGTT3') of VEGF as primers. After completion of the PCR reaction, the 5' ends were phosphorylated and an approximately 600 bp DNA band was separated by 1.2% agarose gel electrophoresis. After polymerization by self-ligation, the cDNA was cut with *EcoRI* and *BamHI* and inserted into the *EcoRI* and *BamHI* sites of vector pUC19. This was used to transform *E. coli* JM83, and plasmids were recovered from the transformed clones. A VEGF cDNA fragment was cut out of the plasmids with *HindIII* and *EcoRI* and then inserted into pIRES2-rsGFP vector and obtain pIRES2-rsGFP/VEGF for protein expression.

[2] Preparation of VEGF high-expressing strain

After overnight culturing of KP-1 human pancreatic cancer cells (3×10^6 cells) with 10% FCS-containing RPMI 1640 medium, an Effectene Transfection Reagent Kit (Qiagen) was used for introduction of 3 μ g of pIRES2-rsGFP/VEGF into the KP-1 cells. After culturing in 10% FCS-containing RPMI 1640 medium containing 600 μ g/ml of Geneticin, drug-resistant cells were selected. Furthermore, GFP high-expressing cells were collected by cell sorter (Becton Dickinson) as VEGF high-expressing KP-1 cells (KP-1/VEGF).

[3] Measurement of VEGF level in culture supernatant

The KP-1/VEGF cells were prepared to 5×10^5 cells/ml,

and 0.5 ml thereof was dispensed into each well of a 24-well plate and cultured at 37°C for 24 hours. The culture supernatants were collected and the VEGF levels thereof measured using a VEGF measuring kit (IBL Co., Ltd.) for confirmation of high expression.

[4] Evaluation of *in vivo* angiogenesis-inducing activity using mouse dorsal air sac model

Millipore rings (Nihon Millipore) were sealed with 0.45 µm Durapore filter membranes (Nihon Millipore) to create chambers. KP-1/VEGF human pancreatic cancer cells (3×10^6) suspended in 0.17 ml of collagen gel were injected into each chamber through the injection port, and the chambers were sealed. Approximately 10 ml of air was then injected in the dorsal skin of 6-week-old C57BL/6N female mice under anesthesia to produce pouches, and the prepared chambers were transplanted therein. About 6 hours after completing transplantation, a test substance suspended in 0.5% methylcellulose was orally administered (0.1 ml/10 g body weight), and this was continued once a day for the next 4 days.

On the 4th day after transplanting the chambers, 0.2 ml of ^{51}Cr (Amersham Pharmacia)-labeled mouse erythrocytes (2.5×10^6 cpm/ml) were injected through the caudal veins of each of the mice with the transplanted chambers. After a prescribed period, the skin in contact with the chamber was excised and frozen, the section in direct contact with

the chamber was precisely cut off, and the radioactivity was measured with a γ -counter. The blood volume was calculated from the radioactivity and used as an index of the *in vivo* angiogenesis-inducing activity. The angiogenesis volume was recorded as this measured blood volume minus the blood volume obtained with transplantation of a chamber containing only collagen gel. The experiment was conducted using 10 mice in the control (solvent-administered) group and 5 mice in each compound-administered group.

[0110]

Pharmacological Test Example 4: Evaluation of antitumor activity on KP-1/VEGF cells in subcutaneous xenograft models

VEGF high-expressing pancreatic cancer cells (KP-1/VEGF) suspended in PBS at a concentration of 1×10^7 cells/ml were transplanted under the right flank skin of 6-week-old female Balb/c (nu/nu) mice in a volume of 0.1 ml. When the tumor volume reached approximately 100 mm^3 , the test substance was orally administered over a period of 2 weeks with a schedule of 5 days per week. The test substance was suspended in 0.5% methylcellulose for an administered volume of 0.1 ml/ 10 g body weight. The tumor size was measured twice a week using a micrometer caliper. The tumor volume was determined by measuring the long and short diameters of the tumor with a micrometer caliper, and calculating $1/2 \times (\text{long diameter} \times \text{short diameter} \times \text{short}$

diameter). The experiment was conducted using 10 mice in the control (solvent-administered) group and 5 mice in each test substance-administered group.

[0111]

5 Pharmacological Test Examples 5: Evaluation of angiogenesis inhibition activity in mouse angiogenesis model by using Matrigel

 The experiment was performed according to the method as already reported in the method (Lab. Invest., 67(4), 519
10 - 528, 1992). Specifically, 10 µg/ml of recombinant FGF-2 (purchased from Invitrogen Corporation) dissolved in PBS was added to Matrigel Matrix (purchased from BD Biosciences) to prepare 1 µg/ml. After that, a 300 µl of this mixture of Matrigel Matrix and Recombinant FGF-2 was injected into
15 a subcutaneous tissue on the median line of the abdomen of a 6-week-old Balb/c (nu/nu) mouse.

 Subsequently, the test substance suspended in a 0.5% methyl cellulose or the like had been orally administered in succession once a day or twice a day for 7 days.

20 After 7 days, the implanted Matrigel was taken out, 300 µl of water was added thereto, and cut into pieces with scissors. The resultant substance was allowed to stand at a cool dark place overnight. After hemoglobin in Matrigel was fully extracted, 100 µl of the supernatant obtained by
25 centrifugation and 100 µl of Drabkin's solution (purchased from Sigma Chemical Co., Ltd) were allowed to react at room

temperature at a dark place for 1 hour. After that, the absorbance of the reaction solution was measured with measured wavelength of 550nm and reference wavelength of 660 nm. The hemoglobin quantity (g/ml) in Matrigel was calculated from the calibration curve established by use of designating hemoglobin as a standard.

The experiment was conducted using 8 mice in the control (solvent-administered) group and 6 mice in each compound-administered group.

[0112]

[Examples]

The compounds according to the present invention can be prepared by the methods as described in the following examples, for example. These are, however, exemplary, and the compounds according to the present invention are not limited to the specific examples mentioned below in any cases.

[0113]

Example 1

N1-Ethyl-5-(2-((methoxylamino)carbonyl)amino-4-pyrimidyl)oxy-1H-1-indolecarboxamide

[0114]

Similarly to Production example 27-2, a crude product of phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyrimidyl)carbamate (546 mg, 1.31 mmol, 56.3%) was obtained as pale

brown powder from

N1-ethyl-5-(2-amino-4-pyrimidyl)oxy-1H-1-indolecarboxamide (691 mg, 2.32 mmol) and phenyl chlorocarbonate. The crude carbamate product (273 mg, 0.65 mmol) was dissolved in tetrahydrofuran (7.0 ml); and triethylamine (0.91 ml, 6.53 mmol) and methoxylamine hydrochloride (273 mg, 3.27 mmol) was added thereto while stirred at room temperature. After the reaction mixture was stirred overnight, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and was dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 1: 1). The crystals were precipitated from ethyl acetate-hexane (1: 10), filtered off, and dried under aeration to yield the title compound (52.5 mg, 0.14 mmol, 21.7%) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.17 (3H, t, J=7.2 Hz), 3.20-3.40 (2H, m), 3.68 (3H, s), 6.45 (1H, d, J=5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.09 (1H, dd, J=2.4, 8.8 Hz), 7.43 (1H, d, J=2.4 Hz), 7.54 (1H, d, J=5.6 Hz), 7.89 (1H, d, J=3.6 Hz), 8.21 (1H, m), 8.26 (1H, d, J=8.8 Hz), 8.34 (1H, d, J=5.6 Hz), 9.31 (1H, d, J=10.0 Hz).

[0115]

The starting materials were synthesized by the following methods.

Production example 1-14-Chloro-6-(1H-5-indolyloxy)-2-pyrimidinamine

[0116]

Sodium hydride (1.0 g, 25 mmol) was suspended in dimethyl sulfoxide (40 ml) under nitrogen atmosphere, and 5-hydroxyindole (3.33 g, 25 mmol) was gradually added while the reaction mixture was stirred at room temperature. After 20 minutes, 2-amino-4,6-dichloropyrimidine (3.28 g, 20 mmol) was added. The reaction mixture was heated at 100 °C and was stirred for 3 hours. After the reaction mixture was cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and 10% aqueous ammonia solution. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. After the solvent was distilled off, the residue was purified by NH silica gel column chromatography (eluent; ethyl acetate: hexane = 2: 1). The crystals were precipitated from ethyl acetate, filtered off, and dried under aeration to yield the title compound (1.15 g, 4.41 mmol, 22.0%) as white crystals.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 5.09 (2H, brs), 6.07 (1H, s), 6.57 (1H, m), 6.95 (1H, dd, J=2.4, 8.8 Hz), 7.29 (1H, m), 7.37 (1H, m), 7.41 (1H, d, J=8.8 Hz), 8.28 (1H, brs).

[0117]

Production example 1-24-(1H-5-Indolyloxy)-2-pyrimidinamine

[0118]

4-Chloro-6-(1H-5-indolyloxy)-2-pyrimidinamine
(1.15 g, 4.41 mmol) was dissolved in tetrahydrofuran (50
ml)-triethylamine (3.07 ml), 10% palladium on carbon (50%
wet, 500 mg) was added, and the reaction mixture was stirred
5 overnight under hydrogen atmosphere at atmospheric
pressure.

The reaction was purged with nitrogen. After
methanol (50 ml) was added and stirred, the catalyst was
filtered out. The resultant solution was concentrated
10 under reduced pressure, thus the title compound (826 mg,
3.65 mmol, 82.8%) was obtained as pale gray powder.

¹H-NMR Spectrum (CDCl₃) δ(ppm): 4.96 (2H, brs), 6.06 (1H,
d, J=5.6 Hz), 6.56 (1H, m), 6.97 (1H, dd, J=2.4, 8.8 Hz),
7.26-7.28 (1H, m), 7.38-7.42 (2H, m), 8.08 (1H, d, J=8.8
15 Hz), 8.29 (1H, brs).

[0119]

Production example 1-3

N1-Ethyl-5-(2-amino-4-pyrimidyl)oxy-1H-1-indolecarboxam
ide

[0120]

Sodium hydride (157 mg, 3.93 mmol) was suspended in
N,N-dimethylformamide (10 ml) under nitrogen atmosphere,
and 4-(1H-5-indolyloxy)-2-pyrimidinamine (826 mg, 3.65
mmol) was gradually added while the reaction mixture was
25 stirred at room temperature. After 10 minutes, the reaction
mixture was cooled with an ice-water bath, phenyl

N-ethylcarbamate (633 mg, 3.83 mmol) was added, the reaction mixture was heated to room temperature, and the solution was stirred for 4 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel chromatography (eluent; ethyl acetate: hexane = 3: 1 to 4: 1) to yield the title compound (691 mg, 2.32 mmol, 63.7%) as white powder.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.32 (3H, t, J=7.2 Hz), 3.54 (2H, m), 4.94 (2H, brs), 5.50 (1H, brs), 6.11 (1H, dd, J=2.4, 5.6 Hz), 6.62 (1H, d, J=3.6 Hz), 7.09 (1H, dd, J=2.4, 8.8 Hz), 7.34 (1H, d, J=2.4 Hz), 7.46 (1H, d, J=3.6 Hz), 8.11 (1H, d, J=5.6 Hz), 8.15 (1H, d, J=8.8 Hz).

[0121]

Example 2

5-(6-(3-(3-Diethylaminopropylamino)ureido)pyrimidin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0122]

Phenyl

(6-(1-methylcarbamoyl-1H-indol-5-yloxy)pyrimidin-4-yl) carbamate (161 mg, 0.400 mmol) was dissolved in N,N-dimethylformamide (1.0 ml), and 3-(diethylamino)propylamine (130 mg, 1.00 mmol) was added while the reaction mixture was stirred at room temperature. After the reaction mixture was stirred overnight, the

reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by NH silica gel column chromatography (eluent; ethyl acetate: methanol = 50: 1). The crystals were precipitated from ethyl acetate-hexane, filtered off, and dried under aeration to yield the title compound (123 mg, 0.280 mmol, 70%) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.93 (6H, t, J=7.0 Hz), 1.52 (2H, m), 2.32-2.46 (6H, m), 2.84 (3H, d, J=3.6 Hz), 3.12 (2H, m), 6.69 (1H, d, J=3.6 Hz), 6.98 (1H, s), 7.06 (1H, dd, J=2.2, 8.8 Hz), 7.37-7.46 (2H, m), 7.88 (1H, d, J=3.6 Hz), 8.18 (1H, m), 8.27 (1H, d, J=8.8 Hz), 8.37 (1H, s), 9.49 (1H, brs).

[0123]

The starting materials were synthesized by the following methods.

Production example 2-1

Phenyl N-methylcarbamate

[0124]

Methylamine hydrochloride (16.9 g, 250 mmol) was dissolved in N,N-dimethylformamide (250 ml), pyridine (44 ml, 275 mmol) was added thereto, and the reaction mixture was stirred. The reaction mixture was cooled with ice, phenyl chloroformate (35 ml, 275 mmol) was added dropwise

thereto, and the reaction mixture was then stirred at room temperature for 24 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The obtained crystals were suspended in diethylether, diluted with hexane, filtered off, washed with the diethylether: hexane = 1: 1, and dried by evacuation, to yield the title compound (22.3 g, 147 mmol, 59.1%) as colorless crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.64 (3H, d, J=3.6 Hz), 7.07 (2H, d, J=8.0 Hz), 7.17 (1H, t, J=8.4 Hz), 7.35 (2H, dd, J=8.0 Hz, 8.4 Hz), 7.58 (1H, d, J=3.6 Hz).

[0125]

Production example 2-2

6-(1H-Indol-5-yloxy)pyrimidin-4-ylamine

[0126]

Sodium hydride (400 mg, 10.0 mmol) was suspended in dimethyl sulfoxide (20 ml) under nitrogen atmosphere, and 5-hydroxyindole (1.33 g, 10.0 mmol) was gradually added while the reaction mixture was stirred at room temperature. After 20 minutes, 6-chloropyrimidin-4-ylamine (1.04 g, 8.00 mmol) was added thereto, the reaction mixture was heated at 100 °C and stirred for 1 hour. After the reaction mixture was naturally cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The

organic layer was washed with water and brine, and was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 3: 1) to yield the title compound (1.07 g, 4.73 mmol, 59%) as a brown oil.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 5.54 (1H, s), 6.43 (1H, m), 6.71 (2H, brs), 6.85 (1H, dd, J=2.4, 8.8 Hz), 7.29 (1H, d, J=2.4 Hz), 7.40-7.45 (2H, m), 8.06 (1H, s), 11.20 (1H, brs).

[0127]

Production example 2-3

5-(6-Aminopyrimidin-4-yloxy)-1H-indol-1-carboxylic acid methylamide

[0128]

Sodium hydride (199 mg, 4.97 mmol) was suspended in N,N-dimethylformamide (10 ml) under nitrogen atmosphere, 6-(1H-indol-5-yloxy)pyrimidin-4-ylamine (1.07 g, 4.73 mmol) synthesized in Production example 2-2 was gradually added while the reaction mixture was stirred at room temperature. After 30 minutes, the reaction mixture was cooled with an ice water bath, then phenyl N-methylcarbamate (751 mg, 4.97 mmol) synthesized in Production example 2-1 was added. The reaction mixture was heated to room temperature and stirred for 1 hour. The reaction mixture was partitioned between ethyl acetate and water. The

organic layer was washed with water and brine, and was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography (eluent; ethyl acetate) to yield the title compound (847 mg, 2.99 mmol, 63%) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.85 (3H, d, J=4.0 Hz), 5.62 (1H, s), 6.68 (1H, d, J=3.6 Hz), 6.77 (2H, brs), 7.04 (1H, dd, J=2.4, 9.2 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.07 (1H, s), 8.15 (1H, q, J=4.0 Hz), 8.27 (1H, d, J=9.2 Hz).

[0129]

Production example 2-4

Phenyl

(6-(1-methylcarbamoyl-1H-indol-5-yloxy)pyrimidin-4-yl)c
arbamate

[0130]

5-(6-Aminopyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide (847 mg, 2.99 mmol) synthesized in Production example 2-3 was dissolved in N,N-dimethylformamide (10 ml) under nitrogen atmosphere. Pyridine (0.290 ml, 11.5 mmol) and phenyl chlorocarbonate (0.394 ml, 3.15 mmol) were sequentially added dropwise thereto while cooling with an ice water bath. After the reaction mixture was stirred for 30 minutes, triethylamine (0.417 ml, 2.99 mmol) was added, and the reaction mixture was heated to room temperature while stirred. After 30

minutes, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and was dried over anhydrous magnesium sulfate. The solvent was distilled off, and then the residue was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 3: 1). The crystals were precipitated from ethyl acetate-hexane, filtered off, and dried under aeration to yield the title compound (504 mg, 1.25 mmol, 42%) as white crystals.

¹H-NMR Spectrum (CDCl₃) δ(ppm): 3.05 (3H, d, J=4.8 Hz), 5.53 (1H, q, J=4.8 Hz), 6.58 (1H, d, J=4.0 Hz), 7.08 (1H, dd, J=2.4, 8.8 Hz), 7.13-7.19 (2H, m), 7.23-7.29 (1H, m), 7.34 (1H, d, J=2.4 Hz), 7.36-7.44 (3H, m), 7.52 (1H, s), 8.14 (1H, d, J=8.8 Hz), 8.59 (1H, s), 9.99 (1H, brs).

[0131]

Example 3

5-(6-(((4-Hydroxypiperidin-1-yl)carbonyl)amino)pyrimidin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0132]

Similarly to Example 2, the title compound (100 mg, 0.231 mmol, 58%) was obtained as white powder from phenyl (6-(1-methylcarbamoyl-1H-indol-5-yloxy)pyrimidin-4-yl) carbamate (161 mg, 0.400 mmol) and 4-hydroxypiperidine.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.24-1.34 (2H, m), 1.64-1.73 (2H, m), 2.85 (3H, d, J=4.0 Hz), 3.02-3.12 (2H, m), 3.64 (1H, m), 3.72-3.80 (2H, m), 4.69 (1H, d, J=4.0 Hz),

6.68 (1H, d, J=3.6 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.20 (1H, s), 7.40 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=3.6 Hz), 8.17 (1H, q, J=4.0 Hz), 8.27 (1H, d, J=8.8 Hz), 8.40 (1H, s), 9.72 (1H, brs).

5 [0133]

Example 4

5-(6-((4-(Pyrrolidin-1-yl)piperidin-1-yl)carbonylamino)pyrimidin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

10 [0134]

Similarly to Example 2, the title compound (141 mg, 0.304 mmol, 76%) was obtained as white crystals from phenyl (6-(1-methylcarbamoyl-1H-indol-5-yloxy)pyrimidin-4-yl) carbamate (161 mg, 0.400 mmol) and 4-(1-pyrrolidynyl)piperidine.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.23-1.36 (2H, m), 1.63-1.70 (4H, m), 1.74-1.84 (2H, m), 2.08-2.18 (1H, m), 2.42-2.50 (4H, m), 2.82-2.95 (5H, m), 3.90-3.98 (2H, m), 6.68 (1H, d, J=3.6 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.20 (1H, s), 7.40 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=3.6 Hz), 8.17 (1H, q, J=4.0 Hz), 8.27 (1H, d, J=8.8 Hz), 8.40 (1H, s), 9.71 (1H, brs).

[0135]

Example 5

25 5-(2-(3-((1R)-1-Carbamoyl-2-phenylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0136]

Phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol) and triethylamine (1 ml) were dissolved in N,N-dimethylformamide (3 ml), and (2R)-2-amino-3-phenylpropionamide hydrochloride (201 mg, 1.00 mmol) was added, and the reaction mixture was stirred for 18 hours. The reaction mixture was partitioned between ethyl acetate and the saturated aqueous solution of ammonium chloride. The organic layer was washed with water and brine, and was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: methanol = 50: 1). The crystals were precipitated from a solvent mixture of ethyl acetate-hexane, filtered off, and dried under aeration to yield the title compound (77.2 mg, 0.152 mmol, 76%) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.81 (1H, dd, J=8.0, 13.2 Hz), 2.84 (3H, d, J=4.4 Hz), 3.01 (1H, dd, J=4.8, 13.2 Hz), 4.38 (1H, m), 6.52 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.2 Hz), 6.86 (1H, s), 7.01-7.07 (2H, m), 7.15-7.30 (5H, m), 7.37 (1H, d, J=2.4 Hz), 7.50 (1H, s), 7.88 (1H, d, J=3.2 Hz), 8.02 (1H, d, J=6.0 Hz), 8.18 (1H, q, J=4.4 Hz), 8.22-8.34 (2H, m), 9.11 (1H, s).

[0137]

The starting material, Phenyl N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)pyridin-2-yl)-N-(phenoxycarbonyl) carbamate, was synthesized as follows.

5 Production example 5-1

N1-Methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxami
de

[0138]

Sodium hydride (430 mg, 10.75mmol) was suspended in
10 N,N-dimethylformamide (25 ml) under nitrogen atmosphere,
and 4-(1H-5-indolyloxy)-2-pyridinamine (2.253 g, 10.00
mmol, CAS No. 417722-11-3) described in WO 02/32872 was
gradually added while stirred at room temperature. After
10 minutes, the reaction mixture was cooled with an ice water
15 bath, and then phenyl N-methylcarbamate (1.587 g, 10.50 mmol)
was added. The reaction mixture was heated to room
temperature and stirred for 2 hours. The reaction mixture
was partitioned between ethyl acetate and water. The
organic layer was washed with water and brine, and was dried
20 over anhydrous sodium sulfate. The solvent was removed by
distilled off. The crystals were precipitated from ethyl
acetate, filtered off, and dried under aeration to yield
the title compound (2.163 g, 7.66 mmol, 76.6%) as pale brown
crystals.

25 ¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.09 (3H, d, J=4.8 Hz), 4.36
(2H, m), 5.49 (1H, m), 5.92 (1H, d, J=2.0 Hz), 6.30 (1H,

dd, J=2.0, 6.0 Hz), 6.61 (1H, d, J=3.6 Hz), 7.07 (1H, dd, J=2.4, 8.8 Hz), 7.30 (1H, d, J=2.4 Hz), 7.45 (1H, d, J=3.6 Hz), 7.92 (1H, d, J=6.0 Hz), 8.17 (1H, d, J=8.8 Hz).

[0139]

5 Production example 5-2

phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate

[0140]

10 N1-Methyl-5-(2-amino-pyridyl)oxy-1H-1-indolecarboxamide (2.0 g, 7.1 mmol) was suspended in tetrahydrofuran (140 ml) and N,N-dimethylformamide (1.4 ml) at room temperature, and triethylamine (2.2 ml, 16 mmol) was added while stirred. The reaction mixture was cooled with an ice,
15 and phenyl chloroformate (1.8 ml, 15 mmol) was added, and the reaction mixture was stirred at room temperature for 1.5 hours. Phenyl chloroformate (0.5 ml) was further added, and the reaction mixture was stirred at room temperature for 0.5 hours. Brine was added to the reaction mixture;
20 and this was subjected to extraction with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the residue, then the precipitated crystals were filtered off, washed with diethyl ether, and dried under
25 aeration to yield the title compound (3.3 g, 6.3 mmol, 89%) as pale brown crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 3.30 (3H, d, J=4.4 Hz), 6.66 (1H, d, J=3.6 Hz), 6.95 (1H, dd, J=2.4, 6.0 Hz), 7.10 (1H, dd, J=2.4, 8.8 Hz), 7.15-7.18 (4H, m), 7.27-7.31 (2H, m), 7.40-7.45 (5H, m), 7.52 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=3.6 Hz), 8.17 (1H, q, J=4.4 Hz), 8.31 (1H, d, J=8.8 Hz), 8.41 (1H, d, J=6.0 Hz).

[0141]

N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide described in Production example 5-1, can be also synthesized as follows.

N1-Methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0142]

5-(2-Aminopyridin-4-yloxy)-2,3-dihydro-1H-indole-1-carboxylic acid methylamide (40 mg, 0.14 mmol) was dissolved in acetic acid (0.9 ml), manganese (III) acetate (29 mg, 0.17 mmol) was added thereto and the reaction mixture was stirred at 70 °C for 3.5 hours. Manganese (III) acetate (29 mg, 0.17 mmol) was further added, and the reaction mixture was further stirred at 70 °C for 0.5 hours. After naturally cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and saturated aqueous solution of sodium hydrogencarbonate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained crystals were suspended in diethyl ether: acetone = 3: 1,

filtered off, washed with diethyl ether, and dried under aeration to yield the title compound (24 mg, 0.085 mmol, 61%) as colorless crystals.

[0143]

5 The starting material,
5-(2-Aminopyridin-4-yloxy)-2,3-dihydro-1H-indole-1-carb
oxylic acid methylamide was synthesized as follows.

Production example 5-3

5-Benzyloxy-1H-indole-1-carboxylic acid methylamide

10 [0144]

Sodium hydride (2.212 g, 55.30 mmol, 60% in oil) was
suspended in N,N-dimethylformamide (100 ml),
5-benzyloxyindole (10.29 g, 46.09 mmol) was added thereto
while stirred at room temperature, and the reaction mixture
15 was stirred at room temperature for 40 minutes. The reaction
mixture was cooled with an ice water bath, and phenyl
N-methylcarbamate (8.360 g, 55.30 mmol) was added. After
the reaction mixture was stirred for 30 minutes, the solution
was stirred at room temperature for 2.5 hours. After water
20 was added to the reaction mixture and the reaction mixture
was stirred at room temperature for 1 hour, the crystals
were sequentially washed with water and diethyl ether, and
dried under aeration to yield the title compound (12.07 g,
43.06 mmol, 93.41%) as pale yellow crystals.

25 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.80 (3H, d, J=4.4 Hz),
5.10 (2H, s), 6.56 (1H, d, J=3.8 Hz), 6.93 (1H, dd, J=2.4,

9.0 Hz), 7.16 (1H, d, J=2.4 Hz), 7.30 (1H, t, J=7.2 Hz), 7.37 (2H, t, J=7.2 Hz), 7.45 (2H, d, J=7.2 Hz), 7.74 (1H, d, J=3.8 Hz), 8.00 (1H, m), 8.11 (1H, d, J=9.0 Hz).

[0145]

5 Production example 5-4

5-Hydroxy-2,3-dihydro-1H-indole-1-carboxylic acid
methylamide

[0146]

5-Benzyloxy-1H-indole-carboxylic acid methylamide
10 (10.00 g, 35.67 mmol) was dissolved in methanol (200 ml) and tetrahydrofuran (150 ml), 10% palladium on carbon (0.9 g) was added, and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 9 hours. After the catalyst was removed by filtration, the solvent was
15 distilled off under reduced pressure. The residue was dissolved in ethanol (400 ml), 10% palladium on carbon (0.9 g) was added, then the reaction mixture was stirred at room temperature under hydrogen atmosphere for 26 hours. After the catalyst was removed by filtration, the solvent was
20 distilled off under reduced pressure. The obtained crystals were suspended in diethyl ether, filtered off, washed with diethyl ether, and dried under aeration to yield the title compound (6.522 g, 33.93 mmol, 95.12%) as grayish crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.61 (3H, d, J=4.4 Hz),
25 2.99 (2H, t, J=8.6 Hz), 3.76 (2H, t, J=8.6 Hz), 6.33 (1H, d, J=4.4 Hz), 6.43 (1H, dd, J=2.4, 8.4 Hz), 6.54 (1H, d,

J=2.4 Hz), 7.58 (1H, d, J=8.4 Hz), 8.82 (1H, s).

[0147]

Production example 5-5

5-(2-Aminopyridin-4-yloxy)-2,3-dihydro-1H-indole-1-carb
oxylic acid methylamide

[0148]

Sodium hydride (202 mg, 3.89 mmol, 60% in oil) was suspended in dimethyl sulfoxide (5.0 ml), then 5-hydroxy-2,3-dihydro-1H-indole-1-carboxylic acid methylamide (971 mg, 5.06 mmol) and 2-amino-4-chloropyridine (500 mg, 3.89 mmol) were added at room temperature under nitrogen atmosphere, and the reaction mixture was heated and stirred at 160 °C for 12 hours under nitrogen atmosphere. After naturally cooled down to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, was dried over anhydrous magnesium sulfate, and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia BW-300; eluent: ethyl acetate, ethyl acetate: methanol = 85: 10 in this order). The fractions containing the desired compound were concentrated, and the residue was further purified by silica gel column chromatography (Fuji Silysia NH, eluent; from ethyl acetate to ethyl acetate: methanol = 90: 10). The obtained crystals were suspended in diethyl ether: acetone = 3: 1, filtered off, washed with diethyl

ether, and dried under aeration to yield the title compound (51 mg, 0.18 mmol, 4.6%) as pale green crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.65 (3H, d, J=4.4 Hz), 3.09 (2H, t, J=8.6 Hz), 3.86 (2H, t, J=8.6 Hz), 5.75 (1H, d, J=2.0 Hz), 5.85 (2H, brs), 6.07 (1H, dd, J=2.0, 6.0 Hz), 6.56 (1H, d, J=4.4 Hz), 6.81 (1H, dd, J=2.4, 8.4 Hz), 6.90 (1H, d, J=2.4 Hz), 7.73 (1H, d, J=6.0 Hz), 7.83 (1H, d, J=8.4 Hz).

[0149]

Example 6

5-(2-(3-((1S)-1-Carbamoyl-2-phenylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0150]

N1-Methyl-5-((2-amino-4-pyridyl)oxy)-1H-indolcarboxamide (100 mg, 0.354 mmol) synthesized in Production example 5-1 and triethylamine (0.3 ml) were dissolved in N,N-dimethylformamide (3 ml). Phenyl chlorocarbonate (0.0888 ml, 0.708 mmol) was added dropwise thereto at room temperature and the reaction mixture was stirred for 30 minutes. (2S)-2-Amino-3-phenylpropionamide (290 mg, 1.77 mmol) was added and the reaction mixture was stirred for 3 days. The reaction mixture was partitioned between a solvent mixture of ethyl acetate-tetrahydrofuran and water. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by silica gel

column chromatography (eluent; ethyl acetate: methanol = 20: 1). The crystals were precipitated from a solvent mixture of ethyl acetate-hexane, filtered off, and dried under aeration to yield the title compound (69.4 mg, 0.147 mmol, 41%) as white crystals.

[0151]

Example 7

5-(2-(3-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methanamide

[0152]

tert-Butoxycarbonylaminoacetic acid (876 mg, 5.00 mmol) and N-methylmorpholine (506 mg, 5.00 mmol) were dissolved in tetrahydrofuran (20 ml). After isobutyl chloroformate (683 mg, 5.00 mmol) was added dropwise at below -15 °C and the reaction mixture was stirred for 30 minutes, pyrrolidine (782 mg, 11.0 mmol) was added at below -15 °C and the reaction mixture was further stirred at 0 °C for 30 minutes. The reaction mixture was partitioned between ethyl acetate and 1N aqueous solution of sodium hydroxide. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and brine, and was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the obtained residue was dissolved in a solvent mixture of ethyl acetate (10 ml)-tetrahydrofuran (5 ml). 4N hydrochloric acid Ethyl acetate solution (5 ml) was added and the reaction mixture

was stirred at room temperature for 18 hours. After the solvent was distilled off, ethyl acetate was added to the crude product to precipitate crystals; and the crystals were filtered off and dried under aeration to yield
 5 2-amino-1-(pyrrolidin-1-yl)ethanone hydrochloride (573 mg, 4.16 mmol, 84%) as white crystals.

The title compound (74.7 mg, 0.171 mmol, 86%) was obtained as white crystals from phenyl
 10 N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol) synthesized in Production example 5-2 and the previously obtained 2-amino-1-(pyrrolidin-1-yl)ethanone hydrochloride (165 mg, 1.00 mmol) similarly to Example 5.
¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.71-1.81 (2H, m),
 15 1.83-1.93 (2H, m), 2.85 (3H, d, J=4.0 Hz), 3.26-3.40 (4H, m), 3.90 (2H, d, J=4.4 Hz), 6.55 (1H, dd, J=2.0, 6.0 Hz), 6.69 (1H, d, J=3.4 Hz), 6.94 (1H, d, J=2.0 Hz), 7.06 (1H, dd, J=2.0, 9.0 Hz), 7.38 (1H, d, J=2.0 Hz), 7.89 (1H, d, J=3.4 Hz), 8.05 (1H, d, J=6.0 Hz), 8.12-8.26 (2H, m), 8.30
 20 (1H, d, J=9.0 Hz), 9.28 (1H, s).

[0153]

Example 8

5-(2-(3-(2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yl)oxy)-1H-indole-1-carboxylic acid methylamide
 25

[0154]

4-Hydroxy-4-methylpiperidine hydrochloride (113 mg, 0.745 mmol) was suspended in N,N-dimethylformamide (3 ml), then triethylamine (1 ml) was added; benzotriazole-1-isooxytris(dimethylamino)phosphonium
5 hexafluorophosphate (201 mg, 0.454 mmol) and ((4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)acetic acid (145 mg, 0.378 mmol) were added thereto; and the reaction mixture was stirred at room temperature for 2 hours. After water was added to the
10 reaction mixture, extraction was performed with ethyl acetate-tetrahydrofuran. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia
15 NH silica gel; ethyl acetate, ethyl acetate: methanol = 20:1, 10:1 in this order). After concentration under reduced pressure, the product was solidified with diethyl ether, suspended, filtered off, washed with diethyl ether, and dried under aeration to yield the title compound (137 mg, 0.285
20 mmol, 75.4%) as a colorless amorphous solid.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.10 (3H, s), 1.38-1.44 (4H, m), 2.83 (3H, d, J=3.6 Hz), 3.02 (2H, m), 3.90 (2H, m), 3.96 (2H, d, J=4.0 Hz), 4.37 (1H, s), 6.52 (1H, d, J=5.6 Hz), 6.67 (1H, d, J=3.2 Hz), 6.91 (1H, s), 7.04 (1H, d, J=9.0 Hz),
25 7.36 (1H, s), 7.87 (1H, d, J=3.2 Hz), 8.03 (1H, d, J=5.6 Hz), 8.17 (2H, m), 8.28 (1H, d, J=9.0 Hz), 9.27 (1H, s).

[0155]

The starting materials were synthesized as follows.

Production example 8-1

((4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)amino)acetic acid

[0156]

Methyl aminoacetate hydrochloride (300 mg, 2.3 mmol) was dissolved in N,N-dimethylformamide (4 ml), and then triethylamine (1 ml) was added. Phenyl N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (250 mg, 0.48 mmol) synthesized in Production example 5-2 was added thereto. The reaction mixture was stirred at room temperature for 22 hours. After water was added to the reaction mixture, extraction was performed with a solvent mixture of ethyl acetate-tetrahydrofuran. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia BW-300, ethyl acetate). The obtained pale yellow oil was dissolved in a solvent mixture of tetrahydrofuran (2 ml)-methanol (1 ml), then 4N aqueous solution of lithium hydroxide (0.48 ml) was added, and the reaction mixture was stirred at room temperature for 1 hour. After that, 1N hydrochloric acid (2 ml) was added, and this was subjected to extraction with ethyl acetate-tetrahydrofuran. The

organic layer was washed with brine and dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to yield the title compound (145 mg, 0.38 mmol, 79%) as colorless crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.83 (3H, d, J=3.6 Hz), 3.81 (2H, d, J=5.6 Hz), 6.57 (1H, m), 6.68 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.05 (1H, dd, J=2.0, 9.2 Hz), 7.38 (1H, d, J=2.0 Hz), 7.88 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=5.6 Hz), 8.16-8.30 (3H, m), 9.33 (1H, brs).

[0157]

Production example 8-2

Benzyl (4-hydroxy-4-methylpiperidin-1-yl)carboxylate

[0158]

Benzyl (4-oxopiperidin-1-yl)carboxylate (4.7 g, 20 mmol) was dissolved in tetrahydrofuran (200 ml); methyllithium-diethylether solution (9.0 ml (1.02 M) + 11.6 ml (1.14 M), total 22 mmol) was added dropwise thereto (internal temperature: -60 °C or below) while stirred at -78 °C under nitrogen atmosphere; and then the reaction mixture was stirred for 1.5 hours as it stands. On the other hand, a similar reaction was performed by using piperidin-4-one-1-carboxylate (1.1 g, 5.0 mmol) in another container. After the saturated aqueous solution of ammonium chloride was added to each reaction mixture, the two reaction mixtures were mixed. Extraction was performed with ethyl acetate, washed with brine, dried over anhydrous magnesium

sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (Fuji Silysia BW-300, hexane-ethyl acetate system) to yield the title compound (4.5 g, 18 mmol, 73%) as colorless crystals.

5 ^1H -NMR Spectrum (DMSO-d_6) δ (ppm): 1.10 (3H, s), 1.32-1.44 (4H, m), 3.17 (2H, m), 3.61 (2H, dt, $J=3.6, 9.2$ Hz), 4.34 (1H, s), 5.04 (2H, s), 7.27-7.37 (5H, m).

[0159]

Production example 8-3

10 4-Hydroxy-4-methylpiperidine monohydrochloride

[0160]

Benzyl

(4-hydroxy-4-methylpiperidin-1-yl)carboxylate (4.5 g, 18 mmol) was dissolved in methanol (90 ml), 10% palladium on carbon powder (0.60 g) was added, and the reaction mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration and the resultant solution was concentrated under reduced pressure to yield a crude product of 4-hydroxy-4-methylpiperidine as a pale yellow oil (2.1 g). After the product was dissolved in methanol, 1N hydrochloric acid (17.5 ml) was added and the solvent was distilled off under reduced pressure. The obtained crystals were suspended in acetone, the crystals were filtered off, washed with acetone, and dried under aeration to yield the title compound (2.1 g, 14 mmol, 77%) as colorless crystals.

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¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.14 (3H, s), 1.55-1.69 (4H, m), 3.00 (4H, m), 4.68 (1H, brs), 8.77 (1H, brs), 8.89 (1H, brs).

[0161]

5 Example 9

5-(2-(3-((1S)-1-Carbamoylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0162]

N1-Methyl-5-((2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (100 mg, 0.354 mmol) synthesized in Production example 5-1 and triethylamine (1 ml) were dissolved in tetrahydrofuran (3ml), then phenyl chlorocarbonate (0.0888 ml, 0.708 mmol) was added dropwise at room temperature, and the reaction mixture was stirred for 2 hours. After the solvent was distilled off under reduced pressure, the residue was dissolved in N,N-dimethylformamide (3 ml). (2S)-2-Aminopropionamide hydrochloride (220 mg, 1.77 mmol) and triethylamine (1 ml) were added and the reaction mixture was stirred for 18 hours. The reaction mixture was partitioned between ethyl acetate and a saturated aqueous solution of ammonium chloride. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: methanol = 20: 1). The crystals were precipitated from a solvent mixture of ethyl acetate-hexane, filtered off, and

dried under aeration to yield the title compound (38.5 mg, 0.0971 mmol, 27%) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.21 (3H, d, J=6.8 Hz), 2.85 (3H, d, J=4.0 Hz), 4.17 (1H, m), 6.55 (1H, d, J=5.2 Hz), 6.70 (1H, d, J=3.6 Hz), 6.93 (1H, s), 7.02 (1H, s), 7.06 (1H, dd, J=2.0, 8.8 Hz), 7.39 (1H, d, J=2.0 Hz), 7.46 (1H, s), 7.90 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.2 Hz) 8.11 (1H, brs), 8.20 (1H, q, J=4.0 Hz), 8.30 (1H, d, J=8.8 Hz), 9.21 (1H, brs).

[0163]

Example 10

5-(2-(3-((1S)-1-Carbamoyl-3-methylbutyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0164]

Similarly to Example 9, the title compound (59.5 mg, 0.135 mmol, 38%) was obtained as white crystals from N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (100 mg, 0.354 mmol) synthesized in Production example 5-1 and (2S)-2-amino-4-methylpentanamide hydrochloride (295 mg, 1.77 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.83-0.91 (6H, m), 1.35-1.50 (2H, m), 1.58 (1H, m), 2.85 (3H, d, J=4.4 Hz), 4.17 (1H, m), 6.53 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.8 Hz), 6.92-7.01 (2H, m), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.38 (1H, d, J=2.4 Hz), 7.48 (1H, s), 7.89 (1H, d, J=3.8 Hz) 7.98-8.12 (2H, m), 8.19 (1H, q, J=4.4 Hz), 8.30 (1H,

d, J=8.8 Hz), 9.09 (1H, s).

[0165]

Example 11

5-(2-(3-Carbamoylmethylureido)pyridin-4-yloxy)-1H-indol
5 e-1-carboxylic acid methylamide

[0166]

Similarly to Example 5, the title compound (52.8 mg, 0.138 mmol, 69%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridy
10 l)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol) synthesized in Production example 5-2 and glycineamide hydrochloride (111 mg, 1.00 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.85 (3H, d, J=4.0 Hz), 3.70 (2H, d, J=5.2 Hz), 6.53 (1H, dd, J=2.4, 5.8 Hz), 6.69
15 (1H, d, J=3.4 Hz), 6.92 (1H, d, J=2.4 Hz), 7.01 (1H, s), 7.06 (1H, dd, J=2.4, 9.2 Hz), 7.34-7.42 (2H, m), 7.89 (1H, d, J=3.4 Hz), 8.05 (1H, d, J=5.8 Hz), 8.14-8.26 (2H, m), 8.30 (1H, d, J=9.2 Hz), 9.21 (1H, s).

[0167]

20 Example 12

5-(2-(3-Cyclopropylcarbamoylmethylureido)pyridin-4-ylox
y)-1H-indole-1-carboxylic acid methylamide

[0168]

Similarly to Example 5, the title compound (50.7 mg, 0.120 mmol, 60%) was obtained as white powder from phenyl
25 N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridy

1)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol) synthesized in Production example 5-2 and 2-amino-N-cyclopropylacetamidehydrochloride (151mg, 1.00 mmol) obtained from tert-butoxycarbonylaminoacetic acid and cyclopropylamine by the method similar to Example 7.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.36-0.42 (2H, m), 0.57-0.63 (2H, m), 2.60 (1H, m), 2.85 (3H, d, J=4.4 Hz), 3.68 (2H, d, J=5.2 Hz), 6.53 (1H, dd, J=2.0, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.91 (1H, d, J=2.0 Hz), 7.06 (1H, dd, J=2.4, 9.0 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 8.00 (1H, d, J=4.0 Hz), 8.06 (1H, d, J=6.0 Hz) 8.14-8.26 (2H, m), 8.30 (1H, d, J=9.0 Hz), 9.21 (1H, s).

[0169]

Example 13

5-(2-(3-((1S)-1-Carbamoyl-2-hydroxyethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0170]

Similarly to Example 9, the title compound (52.1 mg, 0.126 mmol, 36%) was obtained as white crystals from N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (100 mg, 0.354 mmol) synthesized in Production example 5-1 and (2S)-2-amino-3-hydroxypropionamide hydrochloride (249 mg, 1.77 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.85 (3H, d, J=4.4 Hz), 3.52 (1H, dd, J=4.8, 6.4 Hz), 3.62 (1H, dd, J=4.8, 6.4 Hz), 4.13 (1H, m), 4.94 (1H, brs), 6.53 (1H, dd, J=2.4, 6.0 Hz),

6.69 (1H, d, J=3.6 Hz), 6.99 (1H, s), 7.02-7.10 (2H, m),
7.35 (1H, s), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6
Hz), 8.05 (1H, d, J=6.0 Hz), 8.10-8.26 (2H, m), 8.30 (1H,
d, J=8.8 Hz), 9.22 (1H, s).

5 [0171]

Example 14

5-(2-(3-((1R)-1-Carbamoyl-2-hydroxyethyl)ureido)pyridin
-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0172]

10 Similarly to Example 9, the title compound (56.0 mg,
0.136 mmol, 68%) was obtained as white crystals from phenyl
N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridy
l)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol)
synthesized in Production example 5-2 and
15 (2R)-2-amino-3-hydroxypropioamide hydrochloride (167 mg,
1.00 mmol) obtained from
(2R)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic
acid and aqueous ammonia by the method similar to Example
7.

20 [0173]

Example 15

(2S)-2-(3-(4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridi
n-2-yl)ureido)-1,5-pentanedicarboxylic acid diamide

[0174]

25 Similarly to Example 6, the title compound (82.5 mg,
0.189 mmol, 51%) was obtained as white powder from

N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (100 mg, 0.354 mmol) synthesized in Production example 5-1 and (2S)-2-amino-1,5-pentanedicarboxylic acid diamide hydrochloride (321 mg, 1.77 mmol).

5 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.66-2.28 (4H, m), 2.85 (3H, d, J=4.4 Hz), 4.17 (1H, m), 6.53 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.72 (1H, s), 6.97 (1H, s), 7.01-7.10 (2H, m), 7.30 (1H, s), 7.38 (1H, d, J=2.4 Hz), 7.49 (1H, s), 7.76 (1H, s) 7.89 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=6.0 Hz), 8.18 (1H, q, J=4.4 Hz), 8.30 (1H, d, J=8.8 Hz), 9.13 (1H, s).

[0175]

Example 16

15 (2S)-2-(3-(4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)ureido)succinamide

[0176]

Similarly to Example 6, the title compound (65.7 mg, 0.150 mmol, 42%) was obtained as white crystals from N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (100 mg, 0.354 mmol) synthesized in Production example 5-1 and (2S)-2-aminosuccinamide hydrochloride (297 mg, 1.77 mmol).

25 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.45 (2H, d, J=6.8 Hz), 2.85 (3H, d, J=3.6 Hz), 4.40 (1H, m), 6.53 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.88 (1H, s), 6.95 (1H, s), 7.00 (1H, d, J=2.4 Hz), 7.06 (1H, dd, J=2.4, 9.2 Hz),

7.28 (1H, s), 7.35 (1H, s), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 8.04 (1H, d, J=6.0 Hz), 8.18 (1H, q, J=4.0 Hz), 8.26 (1H, brs), 8.30 (1H, d, J=9.2 Hz), 9.19 (1H, s).

[0177]

5 Example 17

5-(2-(3-((1S)-1-Cyclopropylcarbamoyl-2-hydroxyethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0178]

10 Similarly to Example 5, the title compound (72.0 mg, 0.159 mmol, 80%) was obtained as white powder from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol) synthesized in Production example 5-2 and
15 (2S)-2-amino-N-cyclopropyl-3-hydroxypropionamide hydrochloride (181 mg, 1.00 mmol) obtained from (2S)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic acid and cyclopropylamine by the method similar to Example 7.

20 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.35-0.44 (2H, m), 0.54-0.63 (2H, m), 2.62 (1H, m), 2.85 (3H, d, J=4.0 Hz), 3.45-3.58 (2H, m), 4.09 (1H, m), 4.91 (1H, t, J=5.2 Hz), 6.53 (1H, dd, J=2.0, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.99 (1H, d, J=2.0 Hz), 7.04 (1H, dd, J=2.4, 8.8 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 7.98 (1H, d, J=4.4 Hz), 8.05 (1H, d, J=6.0 Hz), 8.09-8.24 (2H, m), 8.30 (1H,

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d, J=8.8 Hz), 9.18 (1H, s).

[0179]

Example 18

5-(2-(3-((1S)-1-Hydroxymethyl-2-oxo-2-pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0180]

Similarly to Example 5, the title compound (67.6 mg, 0.145 mmol, 73%) was obtained as white powder from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (104 mg, 0.200 mmol) synthesized in Production example 5-2 and (2S)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride (165 mg, 0.848 mmol) obtained from (2S)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic acid and pyrrolidine by the method similar to Example 7. ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.72-1.81 (2H, m), 1.81-1.90 (2H, m), 2.85 (3H, d, J=4.4 Hz), 3.22-3.36 (2H, m), 3.46-3.60 (4H, m), 4.54 (1H, m), 4.98 (1H, brs), 6.54 (1H, dd, J=2.0, 5.6 Hz), 6.69 (1H, d, J=3.6 Hz), 6.97 (1H, d, J=2.0 Hz), 7.05 (1H, dd, J=2.4, 8.8 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=5.6 Hz), 8.13-8.23 (2H, m), 8.30 (1H, d, J=8.8 Hz), 9.18 (1H, s).

[0181]

Example 19

5-(2-(3-((1R)-1-Hydroxymethyl-2-oxo-2-pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

hyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methylamide

[0182]

Similarly to Example 5, the title compound (305 mg,
 0.654 mmol, 93%) was obtained as white powder from phenyl
 N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridy
 l)-N-(phenoxycarbonyl)carbamate (366 mg, 0.700 mmol)
 synthesized in Production example 5-2 and
 (2R)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one
 hydrochloride obtained from
 (2R)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic
 acid and pyrrolidine by the method similar to Example 7.

[0183]

Example 20

5-(2-(3-((1S)-1-Hydroxymethyl-2-oxo-2-piperidin-1-yleth
yl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
methylamide

[0184]

Similarly to Example 5, the title compound (124 mg,
 0.258 mmol, 86%) was obtained as white crystals from phenyl
 N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridy
 l)-N-(phenoxycarbonyl)carbamate (157 mg, 0.300 mmol)
 synthesized in Production example 5-2 and
 (2S)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one
 hydrochloride (312 mg, 1.50 mmol) obtained from
 (2S)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic

acid and piperidine by the method similar to Example 7.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.36-1.61 (6H, m), 2.85 (3H, d, J=4.4 Hz), 3.40-3.53 (6H, m), 4.76 (1H, m), 4.92 (1H, brs), 6.54 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.97 (1H, d, J=2.4 Hz), 7.06 (1H, dd, J=2.4, 9.0 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.10-8.26 (2H, m), 8.30 (1H, d, J=9.0 Hz), 9.21 (1H, s).

[0185]

10 Example 21

5-(2-(3-((1R)-1-Hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0186]

15 (2R)-2-Benzylloxycarbonylamino-3-hydroxypropionic acid (1.91 g, 8.00 mmol) and N-methylmorpholine (809 mg, 8.00 mmol) were dissolved in tetrahydrofuran (20 ml). After isobutyl chloroformate (1.09 g, 8.00 mmol) was added dropwise at -15 °C or below, the reaction mixture was stirred for 30 minutes. Then, pyrrolidine (1.13 g, 16.0 mmol) was added at -15 °C or below, and the reaction mixture was further stirred at 0 °C for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1N hydrochloric acid, 1N aqueous solution of sodium hydroxide, a saturated aqueous solution of sodium hydrogencarbonate, and brine, and dried over

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anhydrous magnesium sulfate. The solvent was distilled off, and the obtained residue was dissolved in a solvent mixture of methanol (15 ml)-tetrahydrofuran (15 ml). Then, 10% palladium on carbon (wet) (300 mg) was added, and the reaction mixture was stirred at room temperature under the stream of hydrogen for 90 minutes. After the catalyst was removed by filtration, the solvent of the filtrate was distilled off under reduced pressure to yield (2R)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one (684 mg, 3.97 mmol, 50%) as a colorless oil. Similarly to Example 5, the title compound (107 mg, 0.223 mmol, 74%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate (157 mg, 0.300 mmol) synthesized in Production example 5-2 and previously obtained (2R)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one (228 mg, 1.32 mmol).

[0187]

Example 22

5-(2-(3-((1S)-1-Hydroxymethyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0188]

Similarly to Example 5, the title compound (118 mg, 0.238 mmol, 69%) was obtained as white powder from phenyl

N-(4-(1-(methyamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (179 mg, 0.343 mmol) synthesized in Production example 5-2 and (2S)-2-amino-3-hydroxy-1-(4-hydroxypiperidin-1-yl)propan-1-one hydrochloride (385 mg, 1.71 mmol) obtained from (2S)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic acid and 4-hydroxypiperidine by the method similar to Example 7.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.16-1.40 (2H, m), 1.61-1.80 (2H, m), 2.85 (3H, d, J=4.0 Hz), 2.98-3.50 (5H, m), 3.63-3.95 (3H, m), 4.76 (1H, m), 4.92 (1H, brs), 6.55 (1H, dd, J=2.0, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.96 (1H, d, J=2.0 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.38 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.08-8.26 (2H, m), 8.30 (1H, d, J=8.8 Hz), 9.26 (1H, s).

[0189]

Example 23

5-(2-(3-((1S)-1-Hydroxymethyl-2-(morpholin-4-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0190]

Similarly to Example 5, the title compound (121 mg, 0.251 mmol, 84%) was obtained as white crystals from phenyl N-(4-(1-(methyamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (157 mg, 0.300 mmol) synthesized in Production example 5-2 and

(2S)-2-amino-3-hydroxy-1-(morpholin-4-yl)propan-1-one hydrochloride (316 mg, 1.50 mmol) obtained from (2S)-2-(tert-butoxycarbonylamino)-3-hydroxypropionic acid and morpholine by the method similar to Example 7.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.85 (3H, d, J=4.4 Hz), 3.36-3.62 (10H, m), 4.74 (1H, m), 4.92 (1H, brs), 6.54 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.96 (1H, d, J=2.4 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.14-8.28 (2H, m), 8.30 (1H, d, J=8.8 Hz), 9.25 (1H, s).

[0191]

Example 24

5-(2-(3-(2-Cyclopropylcarbamoyl)ethyl)ureido)pyridin-4-ylloxy)-1H-indole-1-carboxylic acid methylamide

[0192]

Similarly to Example 5, the title compound (117 mg, 0.268 mmol, 89%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy)carbamate (157 mg, 0.300 mmol) synthesized in Production example 5-2 and 3-amino-N-cyclopropylpropionamide hydrochloride (247 mg, 1.50 mmol) obtained from 3-(tert-butoxycarbonylamino)propionic acid and cyclopropylamine by the method similar to Example 7.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.32-0.38 (2H, m), 0.54-0.60 (2H, m), 2.19 (2H, t, J=6.4 Hz), 2.60 (1H, m),

2.85 (3H, d, J=4.4 Hz), 3.25-3.33 (2H, m), 6.53 (1H, dd, J=2.0, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.90 (1H, d, J=2.0 Hz), 7.05 (1H, dd, J=2.4, 9.0 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 7.93 (1H, d, J=4.0 Hz), 7.96-8.06 (2H, m), 8.18 (1H, q, J=4.4 Hz), 8.30 (1H, d, J=9.0 Hz), 9.08 (1H, s).

[0193]

Example 25

5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0194]

Similarly to Example 5, the title compound (122 mg, 0.270 mmol, 90%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (157 mg, 0.300 mmol) synthesized in Production example 5-2 and 3-amino-1-(pyrrolidin-1-yl)propan-1-one hydrochloride (268 mg, 1.50 mmol) obtained from 3-(tert-butoxycarbonylamino)propionic acid and pyrrolidine by the same method similar to Example 7.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.70-1.78 (2H, m), 1.80-1.88 (2H, m), 2.40 (2H, t, J=6.2 Hz), 2.85 (3H, d, J=4.4 Hz), 3.24-3.38 (6H, m), 6.52 (1H, dd, J=2.0, 5.6 Hz), 6.69 (1H, d, J=3.6 Hz), 6.92 (1H, d, J=2.0 Hz), 7.05 (1H, dd, J=2.4, 9.0 Hz), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 7.98-8.10 (2H, m), 8.18 (1H, q, J=4.4 Hz), 8.30 (1H,

d, J=9.0 Hz), 9.10 (1H, s).

[0195]

Example 26

5-(2-(3-(3-(4-Hydroxy-4-methylpiperidin-1-yl)-3-oxopropyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0196]

The title compound (177 mg, 0.358 mmol, 71.1%) was obtained as colorless crystals by performing the reaction similar to Example 8 using 3-(3-(4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)ureido)propionic acid (200 mg, 0.503 mmol) and 4-hydroxy-4-methylpiperidine monohydrochloride (114 mg, 0.755 mmol, Production example 8-3).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.07 (3H, s), 1.23-1.41 (4H, m), 2.44 (2H, d, J=4.8 Hz), 2.83 (3H, d, J=4.4 Hz), 2.98 (1H, m), 3.23-3.30 (3H, m), 3.46 (1H, m), 3.93 (1H, m), 4.32 (1H, s), 6.49 (1H, dd, J=2.0, 6.0 Hz), 6.67 (1H, d, J=3.4 Hz), 6.90 (1H, s), 7.03 (1H, dd, J=2.0, 8.8 Hz), 7.35 (1H, d, J=2.0 Hz), 7.87 (1H, d, J=3.4 Hz), 8.00 (2H, m), 8.15 (1H, d, J=4.4 Hz), 8.28 (1H, d, J=8.8 Hz), 9.06 (1H, s).

[0197]

The starting material was synthesized by the following methods.

Production example 26-1

3-(3-(4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-y
1)ureido)propionic acid

[0198]

5 Ethyl 4-aminopropionate hydrochloride (588 mg, 3.8
mmol) was suspended in N,N-dimethylformamide (3.0 ml), and
then 5N aqueous solution of sodium hydroxide (0.77 ml, 3.8
mmol) was added, and the reaction mixture was stirred at
room temperature. Phenyl
N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)-pyridin
10 -2-yl)-N-(phenoxycarbonyl)carbamate (400 mg, 0.77 mmol,
Production example 5-2) was added thereto, and the reaction
mixture was stirred at room temperature for 0.75 hours.
Water was added to the reaction mixture, and this was
subjected to extraction with ethyl acetate-tetrahydrofuran,
15 dried over anhydrous magnesium sulfate, and concentrated
under reduced pressure. The residue was purified by silica
gel column chromatography (Fuji Silysia BW-300, ethyl
acetate) to yield a pale brown oil. This oil was dissolved
in tetrahydrofuran (4.0 ml) and methanol (2.0 ml), 4N aqueous
20 solution of lithium hydroxide (0.77 ml) was added at room
temperature, and the reaction mixture was stirred at room
temperature for 1.5 hours. To the reaction mixture, 1N
hydrochloric acid (3.1 ml) was added while stirred at room
temperature; and this was subjected to extraction with ethyl
25 acetate-tetrahydrofuran, washed with brine, dried over
anhydrous magnesium sulfate, and concentrated under reduced

pressure. A small amount of acetone was added to the obtained amorphous solid, and this solution was diluted with diethyl ether. The crystals were filtered off, washed with diethyl ether, and dried under aeration to yield the title compound (200 mg, 0.50 mmol, 66%) as colorless crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.39 (2H, t, J=6.2 Hz), 2.84 (3H, d, J=4.0 Hz), 3.30 (2H, m), 6.51 (1H, d, J=5.8 Hz), 6.68 (1H, d, J=3.2 Hz), 6.87 (1H, s), 7.05 (1H, d, J=9.0 Hz), 7.37 (1H, s), 7.88 (1H, d, J=3.2 Hz), 8.01 (1H, d, J=5.8 Hz), 8.16 (1H, m), 8.17 (1H, d, J=4.0 Hz), 8.29 (1H, d, J=9.0 Hz), 9.10 (1H, s), 12.24 (1H, s).

[0199]

Example 27

N1-Ethyl-5-(2-(((2-ethoxyethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0200]

Phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (100 mg, 0.24 mmol) was dissolved in N,N-dimethylformamide (1.0 ml), and 2-ethoxyethylamine (0.063 ml, 0.6 mmol) was added while stirred at room temperature. After 1 hour, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. After the solvent was distilled off, the crystals were precipitated from ethyl

acetate-hexane (1:5), filtered off, and dried under aeration to yield the title compound (100 mg, 0.24 mmol, quantitative) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.09 (3H, t, J=7.2 Hz), 1.17 (3H, t, J=7.2 Hz), 3.21-3.45 (8H, m), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.87 (1H, brs), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=2.4 Hz), 7.91 (1H, d, J=3.6 Hz), 8.01 (1H, d, J=5.6 Hz), 8.12 (1H, m), 8.22 (1H, t, J=4.8 Hz), 8.28 (1H, d, J=8.8 Hz), 9.08 (1H, s).

[0201]

The starting materials were synthesized by the following methods.

Production example 27-1

N1-Ethyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0202]

Sodium hydride (573 mg, 14.32 mmol) was suspended in N,N-dimethylformamide (30 ml) under nitrogen atmosphere. 4-(1H-5-Indolyloxy)-2-pyridinamine (3.00 g, 13.32 mmol, CAS No. 417722-11-3) described in WO 02/32872 was gradually added thereto while stirred at room temperature. After 10 minutes, the reaction mixture was cooled with an ice water bath, and phenyl N-ethylcarbamate (2.31 g, 13.98 mmol) was added. The reaction mixture was heated to room temperature and was stirred for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic

layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, then the crystals were precipitated from ethyl acetate, filtered off, and dried under aeration to yield the title compound (3.168 g, 10.69 mmol, 80.3%) as pale brown crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.32 (3H, t, J=7.2 Hz), 2.40-2.50 (2H, m), 5.74 (1H, d, J=2.4 Hz), 5.83 (2H, brs), 6.12 (1H, dd, J=2.4, 5.6 Hz), 6.66 (1H, d, J=3.6 Hz), 7.01 (1H, dd, J=2.4, 8.8 Hz), 7.32 (1H, d, J=2.4 Hz), 7.75 (1H, d, J=5.6 Hz), 7.88 (1H, d, J=3.6 Hz), 8.19 (1H, t, J=5.6 Hz), 8.26 (1H, d, J=8.8 Hz).

[0203]

Production example 27-2

Phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)
carbamate

[0204]

N1-ethyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (3.168 g, 10.69 mmol) synthesized in Production example 27-1 was dissolved in N,N-dimethylformamide (30 ml) under nitrogen atmosphere. Pyridine (1.25 ml, 15.40 mmol) and phenyl chlorocarbonate (1.61 ml, 12.83 mmol) were sequentially added dropwise while cooled with an ice water bath. The reaction mixture was heated to room temperature while stirred. After 1 hour, the reaction mixture was partitioned between ethyl acetate and water. The organic

layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the crystals were precipitated from ethyl acetate, filtered off, and dried under aeration to yield the title compound (1.530 g, 3.67 mmol, 34.4%) as white crystals.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.32 (3H, t, J=7.2 Hz), 3.53 (2H, m), 5.48 (1H, m), 6.58 (1H, d, J=4.0 Hz), 6.62 (1H, dd, J=2.4, 5.6 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.15 (2H, m), 7.20-7.27 (1H, m), 7.30 (1H, d, J=2.4 Hz), 7.37 (2H, m), 7.45 (1H, d, J=4.0 Hz), 7.52 (1H, d, J=2.4 Hz), 8.10-8.15 (3H, m).

[0205]

Example 28

N1-Methyl-5-(2-((4-(2-hydroxy-2-methylpropionyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0206]

N1-Methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (150 mg, 0.53 mmol) synthesized in Production example 5-1 was dissolved in tetrahydrofuran (3 ml). Triethylamine (0.37 ml, 2.66 mmol) and phenyl chlorocarbonate (0.15 ml, 1.2 mmol) were sequentially added dropwise at room temperature, and the reaction mixture was stirred for 30 minutes. 1-(2-Hydroxy-2-methylpropionyl)piperazine (412 mg, 2.39 mmol) and N,N-dimethylformamide (3 ml) were added and the reaction mixture was stirred for 3 days. The reaction

mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: methanol = 95: 5). The crystals were precipitated from diethyl ether-hexane (1: 2), filtered off, and dried under aeration to yield the title compound (189.4 mg, 0.39 mmol, 74.2%) as white crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.28 (6H, s), 2.83 (3H, d, J=4.0 Hz), 3.10-3.50 (8H, m), 5.43 (1H, s), 6.56 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.30 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.08 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.0 Hz), 8.28 (1H, d, J=8.8 Hz), 9.21 (1H, s).

[0207]

1-(2-Hydroxy-2-methylpropionyl)piperazine was synthesized by the following methods.

Production example 28-1

Benzyl

4-(2-hydroxy-2-methylpropionyl)piperazine-1-carboxylate

[0208]

Benzyl piperazine-1-carbamate (2.203 g, 10.0 mmol) was dissolved in tetrahydrofuran (50 ml); 2-hydroxy-2-methylpropionic acid (1.25 g, 12.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (2.30 g, 12.0 mmol),
1-hydroxy-1H-benzotriazole monohydrate (1.84 g, 12.0 mmol)
and triethylamine (3.35 ml, 24.0 mmol) were added; and the
reaction mixture was stirred at room temperature for 7 hours.

5 The reaction mixture was partitioned between ethyl acetate
and 1N hydrochloric acid. The organic layer was washed with
water, a saturated aqueous solution of sodium
hydrogencarbonate and brine, and dried over anhydrous sodium
sulfate. The solvent was distilled off, and dried under
10 reduced pressure to yield the title compound (2.823 g, 9.21
mmol, 92.1%) as a colorless oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.50 (6H, s), 3.52-3.55 (4H,
m), 3.60-3.70 (4H, m), 3.93 (1H, s), 5.16 (2H, s), 7.34-7.38
(5H, m).

15 [0209]

Production example 28-2

1-(2-Hydroxy-2-methylpropionyl)piperazine

[0210]

Benzyl

20 4-(2-hydroxy-2-methylpropionyl)piperazine-1-carbamate
(2.82 g, 9.20 mmol) synthesized in Production example 28-1
was dissolved in methanol (100 ml) under nitrogen atmosphere;
10% palladium on carbon (50% wet, 1.96 g) was added thereto,
the reaction system was purged with hydrogen at atmospheric
25 pressure; and the reaction mixture was stirred overnight.
After the reaction system was purged with nitrogen, the

catalyst was filtered out, and washed with methanol, then the solvent, together with the filtrate and the washing solution, was distilled off. The residue was dried under reduced pressure to yield the title compound (1.58 g, 9.20 mmol, quantitative) as a colorless oil.

¹H-NMR Spectrum (CDCl₃) δ(ppm): 1.49 (6H, s), 2.84-2.94 (4H, m), 3.49 (1H, s), 3.62-3.70 (4H, m).

[0211]

Example 29

N1-Methyl-5-(2-((3-diethylamino)propylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0212]

Similarly to Example 27, the title compound (96.4 mg, 0.22 mmol, 73.3%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (121 mg, 0.30 mmol) and 3-(diethylamino)propylamine.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.91 (6H, t, J=7.2 Hz), 1.50 (2H, m), 2.30-2.44 (6H, m), 2.83 (3H, d, J=4.4 Hz), 3.23 (2H, m), 6.50 (1H, dd, J=2.4, 6.0 Hz), 6.68 (1H, d, J=3.6 Hz), 6.82 (1H, s), 7.04 (1H, dd, J=2.4, 8.8 Hz), 7.37 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.01 (1H, d, J=6.0 Hz), 8.10-8.17 (2H, m), 8.29 (1H, d, J=8.8 Hz), 9.04 (1H, s).

[0213]

The starting material was synthesized as follows.

Production example 29-1PhenylN-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate

5 [0214]

N1-Methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (2.163 g, 7.66 mmol) synthesized in Production example 5-1 was dissolved in N,N-dimethylformamide (50 ml) under nitrogen atmosphere; pyridine (0.93 ml, 11.5 mmol),
10 triethylamine (2.4 ml, 17.24 mmol) and phenyl chlorocarbonate (1.44 ml, 11.5 mmol) were sequentially added dropwise while cooled with an ice water bath; and the reaction mixture was heated to room temperature while stirred. After 1 hour, the reaction mixture was partitioned between ethyl
15 acetate and water. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and then the residue was purified by silica gel column chromatography (eluent; ethyl acetate), precipitated from ethyl acetate-hexane (1: 10), filtered
20 off, and dried under aeration to yield the title compound (2.731 g, 6.79 mmol, 88.6%) as white crystals.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 3.09 (3H, d, J=4.8 Hz), 5.52 (1H, m), 6.62 (1H, d, J=3.6 Hz), 6.98 (1H, dd, J=2.4, 5.6 Hz), 7.01 (1H, d, J=2.4 Hz), 7.11 (1H, dd, J=2.4, 8.8 Hz),
25 7.14-7.40 (7H, m), 7.47 (1H, d, J=3.6 Hz), 8.24 (1H, d, J=8.8 Hz), 8.41 (1H, d, J=5.6 Hz).

[0215]

Example 30

N1-Methyl-5-(2-(((3-4-hydroxypiperidino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

5 [0216]

Similarly to Example 27, the title compound (51.3 mg, 0.11 mmol, 29.5%) was obtained as white crystals from phenyl N-(4-(1-(methylanino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (150 mg, 0.37 mmol, Production example 29-1) and 1-(3-aminopropyl)-4-hydroxypiperidine.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.29-1.38 (2H, m), 1.50-1.55 (2H, m), 1.64-1.68 (2H, m), 1.88-1.92 (2H, m), 2.20-2.24 (2H, m), 2.62-2.66 (2H, m), 2.83 (3H, d, J=4.4 Hz), 3.06-3.12 (2H, m), 3.39 (1H, m), 4.49 (1H, d, J=4.0 Hz), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, s), 7.87 (1H, d, J=3.6 Hz), 8.01 (1H, d, J=5.6 Hz), 8.05 (1H, m), 8.16 (1H, q, J=4.4 Hz), 8.28 (1H, d, J=8.8 Hz), 9.02 (1H, s).

20 [0217]

Example 31

N1-Methyl-5-(2-(((3-(4-methylpiperazino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0218]

25 Similarly to Example 27, the title compound (133.2 mg, 0.29 mmol, 76.8%) was obtained as white crystals from

phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (150 mg, 0.37 mmol, Production example 29-1) and 1-(3-aminopropyl)-4-methylpiperazine.

5 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.53 (2H, m), 2.11 (3H, s), 2.11-2.40 (10H, m), 2.83 (3H, d, J=4.0 Hz), 3.09 (2H, m), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.01 (1H, d, J=5.6 Hz),
10 8.05 (1H, m), 8.16 (1H, q, J=4.0 Hz), 8.28 (1H, d, J=8.8 Hz), 9.01 (1H, s).

[0219]

Example 32

15 5-(2-(3-(4-Oxo-4-(pyrrolidin-1-yl)butyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0220]

The title compound (113 mg, 0.24 mmol, 77%) was obtained as colorless crystals by performing the reaction similar to Example 8 using
20 4-((4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)butyric acid (130 mg, 0.31 mmol) and pyrrolidine (0.053 ml, 0.63 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.64 (2H, m), 1.71 (2H, m), 1.82 (2H, m), 2.20 (2H, t, J=6.8 Hz), 2.83 (3H, d, J=4.0 Hz), 3.09 (2H, q, J=6.8 Hz), 3.22 (2H, t, J=6.8 Hz), 3.33 (2H, m), 6.50 (1H, dd, J=2.4, 5.8 Hz), 6.67 (1H, d, J=3.6

Hz), 6.86 (1H, d, J=2.4 Hz), 7.03 (1H, dd, J=2.4, 9.0 Hz),
7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.00 (1H,
m), 8.03 (1H, d, J=5.8 Hz), 8.16 (1H, m), 8.28 (1H, d, J=9.0
Hz), 9.00 (1H, s).

5 [0221]

The starting material was synthesized by the following
methods.

Production example 32-1

10 4-((4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)
aminocarbonylamino)butyric acid

[0222]

15 Ethyl 4-aminobutyrate hydrochloride (1.0 g, 6.0 mmol)
was suspended in N,N-dimethylformamide (6.7 ml), 5N aqueous
solution of sodium hydroxide (1.2 ml, 6.0 mmol) was added
and the reaction mixture was stirred at room temperature.

Phenyl

20 N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)pyridin-
2-yl)-N-(phenoxy carbonyl) carbamate (700 mg, 1.3 mmol,
Production example 5-2) was added thereto and the reaction
mixture was stirred at room temperature for 1.2 hours. The
reaction mixture was partitioned between ethyl acetate and
water. The organic layer was dried over anhydrous magnesium
sulfate, concentrated under reduced pressure. The residue
was purified by silica gel column chromatography (Fuji
25 Silysia BW-300, ethyl acetate) to yield a pale yellow oil.
This oil was dissolved in tetrahydrofuran (6.0 ml) and

methanol (3.0 ml); 4N lithium hydroxide (1.1 ml) was added thereto at room temperature; and the reaction mixture was stirred at room temperature for 3.5 hours. Moreover, 1N hydrochloric acid (4.4 ml) and water (2 ml) were added thereto while stirred at room temperature; and this was subjected to extraction with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. After the precipitated crystals were suspended in diethyl ether: hexane = 1: 1, the crystals were filtered off, washed with diethyl ether, and dried under aeration to yield the title compound (411 mg, 1.0 mmol, 75%) as colorless crystals.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.63 (2H, m), 2.20 (2H, t, J=7.4 Hz), 2.83 (3H, d, J=4.0 Hz), 3.10 (2H, m), 6.52 (1H, d, J=5.4 Hz), 6.68 (1H, d, J=3.6 Hz), 6.87 (1H, s), 7.04 (1H, dd, J=2.4, 9.0 Hz), 7.37 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=3.6 Hz), 8.03 (2H, m), 8.17 (1H, d, J=4.0 Hz), 8.29 (1H, d, J=9.0 Hz), 9.03 (1H, s), 12.05 (1H, s).

[0223]

Example 33

5-(2-(3-(3-(Cyclopropylcarbamoyl)propyl)ureido)pyridin-4-yloxy)indole-1-carboxylic acid methylamide

[0224]

The title compound (166 mg, 0.37 mmol, 76%) was obtained as colorless crystals by performing the reaction similar to Example 8 using

4-((4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)butyric acid (200 mg, 0.49 mmol, Production example 32-1) and cyclopropylamine (0.028 ml, 0.58 mmol).

5 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.33-0.37 (2H, m), 0.54-0.59 (2H, m), 1.62 (2H, m), 2.02 (2H, t, J=7.4 Hz), 2.58 (1H, m), 2.85 (3H, m), 3.08 (2H, m), 6.53 (1H, dd, J=2.4, 6.0 Hz), 6.70 (1H, d, J=3.6 Hz), 6.88 (1H, d, J=2.4 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.39 (1H, d, J=2.4 Hz), 7.86
10 (1H, d, J=3.6 Hz), 7.90 (1H, d, J=3.6 Hz), 8.04 (1H, m), 8.05 (1H, d, J=6.0 Hz), 8.19 (1H, d, J=4.2 Hz), 8.31 (1H, d, J=8.8 Hz), 9.04 (1H, s).

[0225]

Example 34

15 5-(2-(3-(4-(4-Hydroxy-4-methylpiperidin-1-yl)-4-oxobutyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0226]

The title compound (195 mg, 0.383 mmol, 78.9%) was
20 obtained as colorless crystals by performing the reaction similar to Example 8 using 4-((4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)butyric acid (200 mg, 0.486 mmol, Production example 32-1) and 4-hydroxy-4-methylpiperidine
25 monohydrochloride (110 mg, 0.729 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.08 (3H, s), 1.22-1.44

(4H, m), 1.62 (2H, m), 2.27 (2H, t, J=7.4 Hz), 2.83 (3H, d, J=4.0 Hz), 2.97 (1H, m), 3.08 (2H, m), 3.29 (1H, m), 3.47 (1H, m), 3.89 (1H, m), 4.33 (1H, s), 6.50 (1H, d, J=6.0 Hz), 6.67 (1H, d, J=3.6 Hz), 6.87 (1H, s), 7.04 (1H, d, J=9.2 Hz), 7.36 (1H, s), 7.87 (1H, d, J=3.6 Hz), 8.01 (1H, m), 8.02 (1H, d, J=6.0 Hz), 8.16 (1H, m), 8.28 (1H, d, J=9.2 Hz), 9.00 (1H, m).

[0227]

Example 35

5-(2-(3-(3-(Diethylcarbamoyl)propyl)ureido)pyridin-4-yl oxy)-1H-indole-1-carboxylic acid methylester

[0228]

The title compound (94 mg, 0.20 mmol, 64%) was obtained as colorless crystals by performing the reaction similar to Example 8 using 4-((4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl) aminocarbonylamino)butyric acid (130 mg, 0.31 mmol, Production example 32-1) and diethylamine (0.066 ml, 0.63 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.96 (3H, t, J=7.2 Hz), 1.04 (3H, t, J=7.2 Hz), 1.63 (2H, m), 2.25 (2H, t, J=7.2 Hz), 2.83 (3H, d, J=4.4 Hz), 3.09 (2H, m), 3.22 (4H, m), 6.51 (1H, dd, J=2.0, 5.6 Hz), 6.67 (1H, d, J=3.4 Hz), 6.86 (1H, d, J=2.0 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.4 Hz), 8.02 (2H, m), 8.16 (1H, d, J=4.4 Hz), 8.29 (1H, d, J=8.8 Hz), 9.00 (1H, s).

[0229]

Example 36

5-(2-(3-(3-(Methylcarbamoyl)propyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

5 [0230]

The title compound (107 mg, 0.25 mmol, 69%) was obtained as colorless crystals by performing the reaction similar to Example 8 using 4-((4-(1-methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)butyric acid (150 mg, 0.36 mmol, Production example 32-1) and methylamine hydrochloride (49 mg, 0.73 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.61 (2H, m), 2.03 (2H, t, J=7.6 Hz), 2.51 (3H, d, J=4.4 Hz), 2.83 (3H, d, J=4.0 Hz), 3.06 (2H, q, J=6.4 Hz), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.86 (1H, d, J=2.4 Hz), 7.03 (1H, dd, J=2.4, 9.2 Hz), 7.36 (1H, d, J=2.4 Hz), 7.71 (1H, m), 7.87 (1H, d, J=3.6 Hz), 8.03 (2H, m), 8.16 (1H, d, J=4.4 Hz), 8.28 (1H, d, J=9.2 Hz), 9.01 (1H, s).

20 [0231]

Example 37

N1-Methyl-5-(2-(pyrrolidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0232]

25 Similarly to Example 5, the title compound (265 mg, 0.70 mmol, 69%) was obtained as white crystals from phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (532 mg, 1.02 mmol) synthesized in Production example 5-2 and pyrrolidine (0.42 ml, 5.0 mmol).

5 MS Spectrum (ESI): 380 (M+1), 759 (2M+1)

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.78-1.84 (4H, m), 2.83 (3H, d, J=4.5 Hz), 3.22-3.36 (4H, m), 6.54 (1H, dd, J=2.3, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.3, 8.7 Hz), 7.35 (1H, d, J=2.3 Hz), 7.41 (1H, d, J=2.3 Hz), 7.87 (1H, d, J=3.6 Hz), 8.04 (1H, d, J=5.6 Hz), 8.16 (1H, m), 8.28 (1H, t, J=8.7 Hz), 8.59 (1H, s).

[0233]

Example 38

15 N1-Methyl-5-(2-(piperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0234]

Similarly to Example 5, the title compound (265 mg, 0.674 mmol, 76%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (463 mg, 0.885 mmol) synthesized in Production example 5-2 and piperidine (0.44 ml, 4.4 mmol).

20 MS Spectrum (ESI): 394 (M+1), 787 (2M+1)

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.37-1.57 (6H, m), 2.83 (3H, d, J=4.4 Hz), 3.26-3.45 (4H, m), 6.54 (1H, dd, J=2.4, 5.4 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, dd, J=2.4, 8.8

Hz), 7.30 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.4 Hz), 8.05 (1H, d, J=5.4 Hz), 8.16 (1H, m), 8.28 (1H, t, J=8.8 Hz), 9.05 (1H, s).

[0235]

5 Example 39

N1-Methyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0236]

10 Similarly to Example 27, the title compound (86.7 mg, 0.21 mmol, 21.2%) was obtained as white powder from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (402 mg, 1.0 mmol) synthesized in Production example 29-1 and 4-hydroxypiperidine.

15 ¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.60-1.70 (2H, m), 1.75 (1H, m), 2.83 (3H, d, J=4.4 Hz), 2.95-3.01 (2H, m), 3.55-3.65 (2H, m), 3.71-3.76 (2H, m), 4.64 (1H, d, J=4.0 Hz), 6.53 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.32 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.4 Hz), 8.28 (1H, d, J=8.8 Hz), 9.10 (1H, s).

[0237]

Example 40

25 N1-Methyl-5-(2-(4-oxopiperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0238]

Phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (440 mg, 0.841 mmol) synthesized in Production example 5-2 was dissolved in N,N-dimethylformamide (5 ml); triethylamine (0.543 ml, 3.90 mmol) and 4-piperidone hydrochloride monohydrate (0.530 g, 3.93 mmol) were added thereto; and the reaction mixture was stirred for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was concentrated to yield the title compound (0.202 g, 0.496 mmol, 59%) as a colorless amorphous solid.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 2.32 (4H, t, J=4.9 Hz), 2.82 (3H, d, J=4.3 Hz), 3.68 (4H, t, J=4.9 Hz), 6.55 (1H, dd, J=2.3, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.3, 8.6 Hz), 7.37 (2H, s), 7.87 (1H, d, J=3.6 Hz), 8.09 (1H, d, J=5.6 Hz), 8.17 (1H, s), 8.28 (1H, t, J=8.6 Hz), 9.37 (1H, s).

[0239]

Example 41

5-(2-(((4-Hydroxy-4-methylpiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indole-1-carboxylic acid methylamide

[0240]

4-Hydroxy-4-methylpiperidine monohydrochloride (508 mg, 3.83 mmol, Production example 8-3) was dissolved in N,N-dimethylformamide (8 ml); triethylamine (2 ml) was

added; and the reaction mixture was stirred at room temperature. Phenyl

N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)pyridin-2-yl)-N-(phenoxy-carbonyl)carbamate (500 mg, 0.957 mmol,

5 Production example 5-2) was added and the reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure; and the residue

10 was purified by silica gel column chromatography (Fuji Silysia BW-300, ethyl acetate, ethyl acetate: methanol = 20: 1 then 10: 1). The obtained amorphous solid was crystallized by adding diethyl ether: acetone = 2: 1. Thus obtained crystals were filtered off, washed with diethyl
15 ether, and dried under aeration to yield the title compound (385 mg, 0.909 mmol, 95.0%).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 1.08 (3H, s), 1.33-1.40 (4H, m), 2.83 (3H, d, J=4.4 Hz), 3.14 (2H, m), 3.63 (2H, m), 4.27 (1H, s), 6.53 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.32 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.4 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, m), 8.28 (1H, d, J=8.8 Hz), 9.04 (1H, s).

[0241]

25 Example 42

N1-Methyl-5-(2-((4-(1-hydroxy-1-methylethyl)piperidino)

carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0242]

Similarly to Example 28, the title compound (71.1 mg, 0.16 mmol, 29.7%) was obtained as white crystals from N1-ethyl-5-((2-amino-4-pyridyl)oxy)-1H-1-indolecarboxamide (150 mg, 0.53 mmol) synthesized in Production example 5-1 and 4-(1-hydroxy-1-methylethyl)piperidine (342 mg, 2.39 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.99 (6H, s), 1.03-1.09 (2H, m), 1.30 (1H, m), 1.60-1.64 (2H, m), 2.54-2.61 (2H, m), 2.83 (3H, d, J=4.4 Hz), 4.08 (1H, s), 4.10-4.15 (2H, m), 6.53 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.32 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.0 Hz), 8.27 (1H, d, J=8.8 Hz), 9.04 (1H, s).

[0243]

4-(1-Hydroxy-1-methylethyl)piperidine was synthesized in the following methods.

Production example 42-1Benzyl 4-ethoxycarbonylpiperidine-1-carboxylate

[0244]

4-Ethoxycarbonylpiperidine (1.572 g, 10.0 mmol) was dissolved in tetrahydrofuran (50 ml); triethylamine (2.79 ml, 20.0 mmol) and benzyl chlorocarbonate (1.71 ml, 12.0 mmol) were added dropwise while cooled with an ice water

bath; and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and the saturated aqueous solution of sodium hydrogencarbonate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 1: 3) to yield the title compound (2.315 g, 7.95 mmol, 79.5%) as a colorless oil.

¹H-NMR Spectrum (CDCl₃) δ(ppm): 1.26 (3H, t, J=7.2 Hz), 1.60-1.70 (2H, m), 1.80-2.00 (2H, m), 2.46 (1H, m), 2.80-3.00 (2H, m), 4.00-4.20 (2H, m), 4.15 (2H, q, J=7.2 Hz), 5.13 (2H, s), 7.29-7.38 (5H, m).

[0245]

Production example 42-2

Benzyl

4-(1-hydroxy-1-methylethyl)piperidine-1-carboxylate

[0246]

Benzyl 4-ethoxycarbonylpiperidine-1-carboxylate (2.315 g, 7.95 mmol) synthesized in Production example 42-1 was dissolved in tetrahydrofuran (25 ml) under nitrogen atmosphere; methyl magnesium bromide (0.93 M) in tetrahydrofuran (32.5ml, 30.2mmol) was added dropwise while cooled with an ice water bath; and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and the

saturated aqueous solution of ammonium chloride. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluent; ethyl acetate: hexane = 1: 1) to yield the title compound (1.786 g, 6.44 mmol, 81%) as a colorless oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.18 (6H, s), 1.18-1.27 (2H, m), 1.40-1.48 (1H, m), 1.74-1.78 (2H, m), 2.60-2.80 (2H, m), 4.20-4.40 (2H, m), 5.13 (2H, s), 7.27-7.37 (5H, m).

[0247]

Production example 42-3

4-(1-Hydroxy-1-methylethyl)piperidine

[0248]

Benzyl

4-(1-hydroxy-1-methylethyl)piperidine-1-carboxylate (1.786 g, 6.44 mmol) synthesized in Production example 42-2 was dissolved in methanol (100 ml) under nitrogen atmosphere; 10% palladium on carbon (50% wet, 1.37 g) was added; the reaction system was purged with hydrogen at atmospheric pressure; and the reaction mixture was stirred overnight. After the reaction system was purged with nitrogen, the catalyst was filtered out, and washed with methanol; the solvent, together with the filtrate and the washing solution, was distilled off; and the residue was dried under reduced pressure to yield the title compound (922 mg, 6.44 mmol, quantitative) as pale gray crystals.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.18 (6H, s), 1.26-1.42 (3H, m), 1.74-1.80 (2H, m), 2.57-2.64 (2H, m), 3.14-3.22 (2H, m), 3.48 (1H, s).

[0249]

5 Example 43

5-(2-(((4-(3-Methylcarbamoylpropyl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0250]

10 4-(1-((4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonyl)piperidin-4-yl)butyric acid (170 mg, 0.35 mmol) was dissolved in N,N-dimethylformamide (7.0 ml); methylamine hydrochloride (48 mg, 0.71 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium
15 hexafluorophosphate (314 mg, 0.71 mmol) and triethylamine (0.35 ml) were added thereto; and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous
20 magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia NH silica gel, hexane-ethyl acetate-methanol system). After a small amount of acetone and ethyl acetate were added to the obtained amorphous solid; this solution
25 was diluted with diethyl ether; and the solid portion was filtered off, washed with diethyl ether, and dried under

aeration to yield the title compound (30 mg, 0.061 mmol, 17%) as a colorless amorphous solid.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.87-1.00 (2H, m), 1.13 (2H, m), 1.33 (1H, m), 1.46 (2H, m), 1.57 (2H, m), 1.99 (2H, t, J=7.4 Hz), 2.52 (3H, d, J=4.4 Hz), 2.65 (2H, m), 2.83 (3H, d, J=4.0 Hz), 4.03 (2H, m), 6.53 (1H, d, J=6.0 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, d, J=9.0 Hz), 7.31 (1H, s), 7.35 (1H, s), 7.66 (1H, m), 7.87 (1H, d, J=3.4 Hz), 8.06 (1H, d, J=4.0 Hz), 8.16 (1H, d, J=4.0 Hz), 8.27 (1H, d, J=9.0 Hz), 9.05 (1H, s).

[0251]

The starting materials were synthesized as follows.

Production example 43-1

tert-Butyl

4-(3-ethoxycarbonylpropyl)piperidine-1-carboxylate

[0252]

tert-Butyl

4-(2-(toluene-4-sulfonyloxy)ethyl)piperidine-1-carboxylate (7.55 g, 19.7 mmol, CAS No. 89151-45-1) as described in WO 02/32872 was dissolved in ethanol; diethyl malonate (3.3 ml, 21.3 mmol) and sodium ethoxide (1.45 g, 21.3 mmol) were added; and the reaction mixture was heated to reflux under nitrogen atmosphere for 2.5 hours. After naturally cooled to room temperature, the saturated aqueous solution of ammonium chloride was added; this was subjected to extraction with ethyl acetate, washed with brine, dried over

anhydrous magnesium sulfate, and concentrated under reduced pressure. After the residue was dissolved in dimethyl sulfoxide (20 ml); lithium chloride (1.7 g, 40 mmol) and water (0.36 ml, 20 mmol) were added; and the reaction mixture was stirred at 185 °C for 1.5 hours and further stirred at 195 °C for 2 hours. After naturally cooled to room temperature, the reaction mixture was partitioned between ethyl acetate-brine. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia BW-300, hexane-ethyl acetate system) to yield the title compound (2.60 g, 8.7 mmol, 43%) as a pale yellow oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.02-1.13 (2H, m), 1.23-1.29 (5H, m), 1.39 (1H, m), 1.45 (9H, s), 1.62-1.69 (4H, m), 2.29 (2H, t, J=7.4 Hz), 2.67 (2H, m), 4.07 (2H, m), 4.13 (2H, q, J=7.2 Hz).

[0253]

Production example 43-2

Ethyl 4-(piperidin-4-yl)butyrate

[0254]

tert-Butyl

4-(3-ethoxycarbonylpropyl)piperidine-1-carboxylate (1.2 g, 4.0 mmol, Production example 43-1) was dissolved in trifluoroacetic acid (30 ml), and the reaction mixture was stirred at room temperature for 20 minutes. This was

concentrated under reduced pressure, and was further azeotropically distilled with toluene. The obtained residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was dried over anhydrous magnesium sulfate. In addition, the aqueous layer was concentrated under reduced pressure to dryness; the obtained solid was suspended in tetrahydrofuran; insoluble portion were filtered off, and this solution was added to the previously obtained organic layer. This was purified by silica gel column chromatography (Fuji Silysia NH, hexane-ethyl acetate-methanol system) to yield the title compound (1.15g, quantitative) as a yellow oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.26 (3H, m), 1.28-1.37 (2H, m), 1.40-1.52 (3H, m), 1.64 (2H, m), 1.86 (2H, m), 2.29 (2H, t, J=7.4 Hz), 2.82 (2H, m), 3.35 (2H, m), 4.13 (2H, m).

[0255]

Production example 43-3

5-(2-(((4-(3-Ethoxycarbonylpropyl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0256]

Ethyl 4-(piperidin-4-yl)butyrate (650 mg, 2.0 mmol, Production example 43-2) was suspended in N,N-dimethylformamide (3.35 ml); phenyl N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)-pyridin

-2-yl)-N-(phenoxycarbonyl)carbamate (350 mg, 0.67 mmol, Production example 5-2) was added; and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was partitioned between ethyl acetate and water.

5 The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia BW-300, hexane-ethyl acetate-methanol system) to yield the title compound (271 mg, 0.54 mmol, 80%) as a pale yellow
10 oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.05-1.16 (2H, m), 1.22-1.28 (5H, m), 1.43 (1H, m), 1.62 (2H, m), 1.71 (2H, m), 2.27 (2H, t, J=7.4 Hz), 2.80 (2H, m), 2.95 (3H, d, J=4.4 Hz), 3.99 (2H, m), 4.12 (2H, q, J=7.2 Hz), 6.09 (1H, d, J=4.4 Hz),
15 6.46 (1H, d, J=3.4 Hz), 6.58 (1H, dd, J=2.0, 5.6 Hz), 7.04 (1H, dd, J=2.0, 8.8 Hz), 7.24 (1H, s), 7.28 (1H, d, J=2.0 Hz), 7.32 (1H, d, J=3.4 Hz), 7.54 (1H, d, J=2.0 Hz), 8.03 (1H, d, J=5.6 Hz), 8.20 (1H, d, J=8.8 Hz).

[0257]

20 Production example 43-4

4-(1-((4-(1-Methylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonyl)piperidin-4-yl)butyric acid

[0258]

5-(2-((4-(3-Ethoxycarbonylpropyl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic
25 acid methylamide (271 mg, 0.54 mmol, Production example 43-3)

was dissolved in tetrahydrofuran (3.0 ml) and methanol (1.5 ml); 4N lithium hydroxide (0.54 ml) was added; and the reaction mixture was stirred at room temperature for 3.5 hours. 1N hydrochloric acid (2.2 ml) was added thereto while the stirred at room temperature. After the precipitated crystals were filtered off, the crystals were washed with water and diethyl ether sequentially, and dried under aeration to yield the title compound (170 mg, 0.35 mmol, 66%) as colorless crystals.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.93 (2H, m), 1.16 (2H, m), 1.36 (1H, m), 1.47 (2H, m), 1.58 (2H, m), 2.15 (2H, t, J=7.4 Hz), 2.66 (2H, m), 2.83 (3H, d, J=4.2 Hz), 4.02 (2H, m), 6.53 (1H, d, J=6.0 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, d, J=9.2 Hz), 7.31 (1H, s), 7.35 (1H, s), 7.86 (1H, d, J=3.4 Hz), 8.05 (1H, d, J=6.0 Hz), 8.15 (1H, d, J=4.2 Hz), 8.27 (1H, d, J=9.2 Hz), 9.02 (1H, s).

[0259]

Example 44

5-(2-(((4-(3-Carbamoylpropyl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0260]

4-(Piperidin-4-yl)butanamide (547 mg, 1.41 mmol) was dissolved in N,N-dimethylformamide (3 ml); phenyl N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)-pyridin-2-yl)-N-(phenoxycarbonyl)carbamate (210 mg, 0.402 mmol, the product of Production example 5-2) was added thereto;

and the reaction mixture was stirred at room temperature for 1.5 hour. The reaction mixture was partitioned between ethyl acetate and water; the organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure; and the residue was purified by silica gel column chromatography (Fuji Silysia NH, ethyl acetate-methanol system). The obtained amorphous solid was crystallized by adding diethyl ether. After addition of a small amount of ethanol to make a suspension, this was diluted with hexane. After separation by filtration to obtain crystals, these were rinsed with diethyl ether and dried under aeration. Thus, the title compound was obtained as colorless crystals (157 mg, 0.328 mmol, 81.7%).

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.87-1.00 (2H, m), 1.10-1.16 (2H, m), 1.35 (1H, m), 1.42-1.50 (2H, m), 1.58 (2H, m), 1.98 (2H, t, J=7.4 Hz), 2.65 (2H, m), 2.83 (3H, d, J=4.0 Hz), 4.03 (2H, m), 6.53 (1H, dd, J=2.0, 5.6 Hz), 6.67 (2H, m), 7.03 (1H, dd, J=2.0, 9.0 Hz), 7.20 (1H, s), 7.31 (1H, d, J=2.0 Hz), 7.35 (1H, d, J=2.0 Hz), 7.87 (1H, d, J=3.2 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, m), 8.28 (1H, d, J=9.0 Hz), 9.05 (1H, s).

[0261]

The starting materials were synthesized as follows.

Production example 44-1

tert-Butyl

4-(3-carbamoylpropyl)piperidine-1-carboxylate

[0262]

tert-Butyl

4-(3-ethoxycarbonylpropyl)piperidine-1-carboxylate
(0.60 g, 2.0 mmol, the product of Production example 43-1)
5 and formamide (0.27 ml, 6.7 mmol) were dissolved in
N,N-dimethylformamide (1.0 ml); sodium ethoxide (0.095 g,
1.4 mmol) was added thereto while stirred and heated at 100
°C; the reaction mixture was stirred for 2 hours under
nitrogen atmosphere. After cooled to room temperature, the
10 reaction mixture was partitioned between water and ethyl
acetate. The organic layer was washed with brine, dried
over anhydrous magnesium sulfate, and then the solvent was
distilled off under reduced pressure. The residue was
purified by silica gel chromatography (eluent; hexane-ethyl
15 acetate = 95:5 to 85:15). The title compound was obtained
as a colorless oil (0.38 g, 1.4 mmol, 70%).

¹H-NMR Spectrum (CDCl₃) δ(ppm): 1.03-1.14 (2H, m),
1.26-1.31 (2H, m), 1.35-1.45 (1H, m), 1.46 (9H, s), 1.63-1.71
(4H, m), 2.22 (2H, t, J=7.6 Hz), 2.67 (2H, m), 4.07 (2H,
20 brs), 5.30 (1H, brs), 5.39 (1H, brs).

[0263]

Production example 44-24-(Piperidin-4-yl)butylamide

[0264]

tert-Butyl

4-(3-carbamoylpropyl)piperidine-1-carboxylate (0.38 g,

1.4 mmol, Production example 44-1) was dissolved in trifluoroacetic acid (2 ml) and the reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was concentrated under reduced pressure and then azeotropically distilled with toluene. The residue was partitioned between tetrahydrofuran and a saturated aqueous solution of sodium hydrogencarbonate; and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure; and the residue was purified by silica gel chromatography (Fuji Silysia NH, ethyl acetate-methanol system) to yield the title compound (0.55 g, quantitative) as pale yellow oil.

¹H-NMR Spectrum (DMSO-d₆) δ(ppm): 0.90-1.01 (2H, m), 1.09-1.15 (2H, m), 1.26 (1H, m), 1.45 (2H, m), 1.55 (2H, m), 1.98 (2H, t, J=7.4 Hz), 2.43 (2H, m), 2.91 (2H, m), 6.65 (1H, s), 7.20 (1H, s).

[0265]

Example 45

5-(2-((4-Pyrrolidin-1-yl)carbonyl)piperidin-1-yl)carboxylamino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid methylamide

[0266]

Similarly to Example 5, the title compound (134 mg, 0.273 mmol, 91%) was obtained as white crystals from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate (157 mg, 0.300 mmol)

synthesized in Production example 5-2 and (piperidin-4-yl)-(pyrrolidin-1-yl)methanone (328 mg, 1.50 mmol) obtained from N-benzyloxycarbonylisonipecotic acid and pyrrolidine by the method similar to Example 21.

5 ¹H NMR Spectrum (DMSO-d₆) δ (ppm): 1.35-1.48 (2H, m), 1.56-1.65 (2H, m), 1.71-1.80 (2H, m), 1.82-1.91 (2H, m), 2.61 (1H, m), 2.73-2.84 (2H, m), 2.85 (3H, d, J=4.4 Hz), 3.22-3.28 (2H, m), 3.44-3.50 (2H, m), 4.04-4.12 (2H, m), 6.56 (1H, d, J=6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 7.06 (1H, 10 dd, J=2.4, 9.2 Hz), 7.34 (1H, s), 7.38 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=3.6 Hz), 8.09 (1H, d, J=6.0 Hz) 8.18 (1H, q, J=4.4 Hz), 8.30 (1H, d, J=9.2 Hz), 9.16 (1H, s).

[0267]

Example 46

15 N1-Methyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0268]

Similarly to Example 27, the title compound (88.5 mg, 0.19 mmol, 63.8%) was obtained as white crystals from phenyl 20 N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (121 mg, 0.30 mmol, Production example 29-1) and 4-tetrahydro-1H-1-pyrrolylpiperidine.

[0269]

Phenyl

25 N1-methyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide may

be synthesized by the following methods.

[0270]

Phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (12.1 g, 23.2 mmol) synthesized in Production example 5-2 was dissolved in dimethylformamide (150 ml); 4-tetrahydro-1H-1-pyrrolylpiperidine (14.4 g, 93.3 mmol) was added thereto; and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine and concentrated to about 100 ml. The residue was allowed to be kept cool at 5 °C for overnight to precipitate crystals. The crystals were filtered off, washed with ethyl acetate to yield the title compound (7.8 g, 16.9 mmol, 73%) as white crystals.

¹H NMR Spectrum (DMSO-d₆) δ (ppm): 1.20-1.33 (2H, m), 1.60-1.70 (4H, m), 1.70-1.80 (2H, m), 2.40-2.60 (5H, m), 2.77-2.84 (5H, m), 3.90-4.00 (2H, m), 6.54 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz) 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.31 (1H, s), 7.35 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, m), 8.28 (1H, d, J=8.8 Hz), 9.11 (1H, s).

[0271]

Example 47

N1-Methyl-5-(2-(((4-(piperidin-1-yl)piperidin-1-yl)carb

onyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0272]

Similarly to Example 27, the title compound (94.6 mg, 0.20 mmol, 66.2%) as white crystals was obtained from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (121 mg, 0.30 mmol, Production example 29-1) and 4-piperidinopiperidine.

[0273]

N1-Methyl-5-(2-(((4-(piperidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide may be prepared by the following methods.

[0274]

Phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (15.5 g, 29.7 mmol) synthesized in Production example 5-2 was dissolved in dimethylformamide (180 ml); 4-piperidinopiperidine (20.0 g, 119 mmol) was added thereto; and the reaction mixture was stirred at room temperature for 9 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine and concentrated to about 100 ml. The residue was allowed to be kept cool at 5 °C overnight to precipitate crystals. The crystals were filtered off and washed with ethyl acetate to yield the title compound (4.0 g, 8.4 mmol, 28%) as white crystals. ¹H NMR Spectrum (DMSO-d₆) δ (ppm): 1.20-1.65 (10H, m),

2.31-2.40 (5H, m), 2.66 (2H, m), 2.83 (3H, d, J=4.4 Hz),
 4.08 (2H, m), 6.53 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d,
 J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.31 (1H, d, J=2.4
 Hz), 7.35 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.06
 5 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.4 Hz), 8.28 (1H, d, J=8.8
 Hz), 9.09 (1H, s).

[0275]

Example 48

N1-Methyl-5-(2-((4-ethylpiperazino)carbonyl)amino-4-pyr
 10 idyl)oxy-1H-1-indolecarboxamide

[0276]

Similarly to Example 27, the title compound (73.2 mg,
 0.17 mmol, 57.8%) was obtained as white powder from phenyl
 N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridy
 15 1)carbamate (121 mg, 0.30 mmol, Production example 29-1)
 and 1-ethylpiperazine.

¹H NMR Spectrum (DMSO-d₆) δ (ppm): 0.97 (3H, t, J=7.2 Hz),
 2.25-2.32 (6H, m), 2.83 (3H, d, J=4.0 Hz), 3.20-3.40 (4H,
 m), 6.55 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz),
 20 7.04 (1H, dd, J=2.4, 8.8 Hz), 7.31 (1H, d, J=2.4 Hz), 7.36
 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.07 (1H, d, J=5.6
 Hz), 8.16 (1H, q, J=4.0 Hz), 8.28 (1H, d, J=8.8 Hz), 9.13
 (1H, s).

[0277]

25

Example 49

N1-Methyl-5-(2-((4-(2-hydroxyethyl)piperazino)carbonyl)

amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0278]

Similarly to Example 27, the title compound (97.6 mg, 0.22 mmol, 59.7%) was obtained as pale pink powder from phenyl N-(4-(1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (150 mg, 0.37 mmol, Production example 29-1) and 1-(2-hydroxyethyl)piperazine.

¹H NMR Spectrum (DMSO-d₆) δ (ppm): 2.30-2.40 (6H, m), 2.83 (3H, d, J=4.0 Hz), 3.20-3.40 (4H, m), 3.46 (2H, m), 4.39 (1H, t, J=5.6 Hz), 6.55 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.31 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.0 Hz), 8.27 (1H, d, J=8.8 Hz), 9.12 (1H, s).

[0279]

Example 50N1-Methyl-5-(2-((3-methylsulfonylpropylamino)carbonyl)amino-4-pyridyl)-oxy-1H-1-indolecarboxamide

[0280]

Similarly to Example 28, the title compound (166.8 mg, 0.37 mmol, 70.5%) was obtained as white crystals from N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (150 mg, 0.53 mmol, Production example 5-1) and 3-methylsulfonylpropylamine hydrochloride (410 mg, 2.36 mmol).

¹H NMR Spectrum (DMSO-d₆) δ (ppm): 1.70-1.90 (2H, m), 2.83

(3H, d, J=4.4 Hz), 2.94 (3H, s), 3.04-3.09 (2H, m), 3.17-3.24 (2H, m), 6.52 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.86 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, s), 7.87 (1H, d, J=3.6 Hz), 8.03 (1H, d, J=5.6 Hz), 8.10-8.17 (2H, m), 8.28 (1H, d, J=8.8 Hz), 9.07 (1H, s).

[0281]

Example 51

N1-Methyl-5-(2-((4-(2-dimethylaminoacetyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0282]

Similarly to Example 28, the title compound (189.8 mg, 0.40 mmol, 74.5%) was obtained as white powder from N1-methyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (150 mg, 0.53 mmol, Production example 5-1) and 1-(2-dimethylaminoacetyl)piperazine (500 mg, 2.92 mmol). ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.14 (6H, s), 3.04 (3H, d, J=4.0 Hz), 3.29 (2H, s), 3.20-3.49 (8H, m), 6.56 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.30 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.08 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.0 Hz), 8.28 (1H, d, J=8.8 Hz), 9.24 (1H, s).

[0283]

1-(2-Dimethylaminoacetyl)piperazine was prepared by the following methods.

Production example 51-1

Benzyl 4-(2-dimethylaminoacetyl)piperazine-1-carboxylate

[0284]

Benzyl piperazine-1-carbamate (2.203 g, 10.0 mmol) was dissolved in tetrahydrofuran (50 ml); 2-dimethylaminoacetic acid (1.24 g, 12.0 mmol),
5 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.30 g, 12.0 mmol), 1-hydroxy-1H-benzotriazole monohydrate (1.84 g, 12.0 mmol) and triethylamine (3.35 ml, 24.0 mmol) were added thereto; and the reaction mixture was stirred at room temperature
10 for 7 hours. The reaction mixture was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and brine, dried over anhydrous sodium sulfate, and
15 the residue was purified by NH silica gel column chromatography (eluent; ethyl acetate: hexane = 3: 1) to yield the title compound (954 mg, 3.12 mmol, 31.2%) as a colorless oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.26 (6H, s), 3.11 (2H, s), 3.45-3.65 (8H, m), 5.15 (2H, s), 7.32-7.38 (5H, m).

[0285]

Production example 51-21-(2-Dimethylaminoacetyl)piperazine

[0286]

25 Benzyl
4-(2-dimethylaminoacetyl)piperazine-1-carbamate (954 mg,

3.12 mmol) synthesized in Production example 51-1 was dissolved in methanol (50 ml) under nitrogen atmosphere; 10% palladium on carbon (50% wet, 665 mg) was added thereto; the reaction system was purged with hydrogen at atmospheric pressure; and the reaction mixture was stirred overnight. After the reaction system was purged with nitrogen, the catalyst was filtered out, and washed with methanol. The solvent, together with the filtrate and washing solution, was distilled off, and the residue was dried under reduced pressure to yield the title compound (508 mg, 2.97 mmol, 95.0%) as a colorless oil.

¹H-NMR Spectrum (CDCl₃) δ (ppm): 2.28 (6H, s), 2.80-2.88 (4H, m), 3.11 (2H, s), 3.52-3.62 (4H, m).

[0287]

Example 52

N1-Methyl-5-(2-((4-cyclohexylpiperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0288]

Similarly to Example 27, the title compound (121.3 mg, 0.25 mmol, 68.2%) was obtained as white crystals from phenyl

N-(4-(1-methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl) carbamate (150 mg, 0.37 mmol, Production example 29-1) and 1-cyclohexylpiperazine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.00-1.20 (6H, m), 1.53 (2H, m), 1.60-1.80 (4H, m), 2.19 (2H, m), 2.30-2.45 (5H,

m), 2.83 (3H, d, J=4.0 Hz), 6.54 (1H, dd, J=2.4, 5.6 Hz),
 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.31
 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6
 Hz), 8.06 (1H, d, J=5.6 Hz), 8.16 (1H, q, J=4.0 Hz), 8.27
 5 (1H, d, J=8.8 Hz), 9.09 (1H, s).

[0289]

Example 53

N4-(4-(1-(Methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide

10 [0290]

Similarly to Example 27, the title compound (58.6 mg,
 0.15 mmol, 49.4%) was obtained as white powder from phenyl
 N-(4-((1-((methylamino)carbonyl)-1H-5-indolyl)oxy-2-pyr
 idyl)carbamate (121 mg, 0.30 mmol, Production example 29-1)
 15 and morpholine.

[0291]

N4-(4-(1-(Methylamino)carbonyl-1H-5-indolyl)oxy-2
 -pyridyl)-4-morpholinecarboxamide may be prepared by the
 following methods.

20 [0292]

Phenyl

N-(4-(1-(methylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (20 g, 38 mmol)
 synthesized in Production example 5-2 was dissolved in
 25 N,N-dimethylformamide (190 ml); morpholine (13.3 mg, 153
 mmol) was added thereto; and the reaction system was stirred

at room temperature for 9 hours. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The
5 obtained residue was dissolved in ethyl acetate and a small amount of tetrahydrofuran; this suspension was filtrated with silica gel; and ethyl acetate and three different ratio of solvent mixtures of ethyl acetate: methanol = 20: 1, 10: 1, and 5: 1 were eluted through the gel. The filtrate was
10 concentrated under reduced pressure. The residue was dissolved in diethyl ether (40 ml); hexane (200 ml) was added thereto; and precipitated insoluble syrupy portion was removed from the solution; and the resultant solution was concentrated again under reduced pressure. The residue was
15 dissolved in ethyl acetate (300 ml) and was allowed to stand at room temperature. After the crystals were precipitated, the crystals were filtered off, washed with ethyl acetate, and dried to yield the crude crystals of the title compound (10.3 g). 9 g of this crude crystals was suspended in a
20 mixture of tetrahydrofuran (3 ml) and N,N-dimethylformamide (3 ml each); this suspension was diluted with ethanol (60 ml); and the crystals were filtered off, washed with ethanol and dried to yield the title compound as colorless crystals (7.70 g, 19 mmol).

25 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.83 (3H, d, J=4.4 Hz), 3.34-3.38 (4H, m), 3.50-3.53 (4H, m), 6.56 (1H, dd. J=2.4,

5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.04 (1H, dd, J=2.4, 8.8 Hz), 7.31 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.08 (1H, d, J=5.6 Hz), 8.17 (1H, q, J=4.4 Hz), 8.28 (1H, d, J=8.8 Hz), 9.19 (1H, s).

[0293]

Example 54

N1-Methyl-5-(2-((1,1-dioxothiomorpholin-4-ylcarbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0294]

Phenyl

N-(4-(1-(methylamino)carbonyl-1H-indol-5-yloxy)-pyridin-2-yl)-N-(phenoxycarbonyl)carbamate (150 mg, 0.278 mmol, Production example 5-2) was dissolved in N,N-dimethylformamide (1.5 ml); 5N aqueous solution of sodium hydroxide (0.29 ml) and 1,1-dioxothiomorpholine hydrochloride (246 mg, 1.44 mmol) were added thereto; and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia BW-300, ethyl acetate). Diethyl ether was added to this to allow to crystallize; and the crystals were filtered off, washed with diethyl ether, and dried under aeration to yield the title compound as colorless crystals (100 mg, 0.226 mmol, 78.5%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.83 (3H, d, J=3.6 Hz),
3.10 (4H, m), 3.81 (4H, m), 6.57 (1H, dd, J=1.2, 5.6 Hz),
6.67 (1H, d, J=3.2 Hz), 7.03 (1H, dd, J=2.0, 9.2 Hz), 7.32
(1H, m), 7.36 (1H, d, J=2.0 Hz), 7.87 (1H, d, J=3.2 Hz),
8.09 (1H, d, J=5.6 Hz), 8.16 (1H, d, J=3.6 Hz), 8.28 (1H,
d, J=9.2 Hz), 9.54 (1H, s).

[0295]

The starting material was synthesized by the following
methods.

Production examples 54-1

tert-Butyl thiomorpholine-4-carboxylate

[0296]

Thiomorpholine (5.0 ml, 53 mol) was dissolved in
tetrahydrofuran (200 ml); triethylamine (8.1 ml, 58 ml) was
added thereto; and the reaction mixture was stirred at room
temperature. tert-Butoxycarbonyl dicarbonate (13.3 ml, 58
mmol) was added thereto and the reaction mixture was stirred
at room temperature for 10 hours. The reaction mixture was
concentrated under reduced pressure; and the residue was
purified by silica gel column (eluent; hexane: ethyl acetate
= from 80: 20, 75: 25 to 70: 30) to yield the title compound
as colorless crystals (10.4 g, 51 mmol).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.46 (9H, s), 2.57 (4H,
m), 3.69 (4H, m).

[0297]

Production example 54-2

tert-Butyl 1,1-dioxothiomorpholine-4-carboxylate

[0298]

tert-Butyl thiomorpholine-4-carboxylate (1.91 g, 9.42 mol) was dissolved in dichloromethane (50 ml);
5 m-chloroperbenzoic acid (5.0 g, 19 mmol) was gradually added while cooled with ice bath, stirred, and under nitrogen atmosphere; and the reaction mixture was stirred at room temperature for 12 hours. After addition of a saturated aqueous solution of sodium thiosulfate, the reaction mixture
10 was kept stirred for a while; and this was subjected to extraction with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Triethylamine (8.1 ml, 58 ml) were added to the obtained crystals; and the reaction mixture was stirred at
15 room temperature. tert-Butoxycarbonyl dicarbonate (13.3 ml, 58 mmol) was added thereto; and the reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was concentrated under reduced pressure; and the obtained crystals were suspended with a solvent mixture of
20 diethyl ether: ethanol = 10: 1, filtered off, washed with diethyl ether and dried under aeration to yield the title compound as colorless crystals (2.03 g, 8.63 mmol, 91.6%).
¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.40 (9H, s), 3.09 (4H, t, J=5.2 Hz), 3.72 (4H, t, J=5.2 Hz).

[0299]

Production example 54-3

Thiomorpholine 1,1-dioxide monohydrochloride

[0300]

tert-Butyl 1,1-dioxothiomorpholine-4-carboxylate (2.03 g, 8.63 mmol) was dissolved in a mixture of hydrochloric acid-methanol 10 (20 ml) and tetrahydrofuran (20 ml); hydrochloric acid (4.0 ml) was added thereto during stirring at room temperature; and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated; methanol (20 ml), tetrahydrofuran (20 ml) and hydrochloric acid (4.0 ml) were added to the obtained crystals. Furthermore, water (10 ml) was added to this solution to perfectly dissolve the crystals; and this solution was stirred at room temperature for 1 hour. The solvent was concentrated under reduced pressure; and the obtained crystals were suspended in methanol, filtered off, washed with methanol, and dried under aeration to yield the title compound as colorless crystals (1.49 g, 8.65 mmol, quantitative).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 3.54 (8H, m), 9.83 (2H, brs).

[0301]

Example 55

5-(2-(3-((1R)-1-Hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide

[0302]

Similarly to Example 5, the title compound (118 mg, 0.246 mmol, 82%) was obtained as white crystals from phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyloxy-2-pyridyl)-N-(phenoxy carbonyl) carbamate (161 mg, 0.300 mmol), and (2R)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one (265 mg, 1.67 mmol) obtained by the method similar to Example 21 from (2R)-2-benzyloxycarbonylamino-3-hydroxypropionic acid and pyrrolidine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.19 (3H, t, J=7.2 Hz), 1.70-1.90 (4H, m), 3.20-3.60 (8H, m), 4.54 (1H, m), 4.98 (1H, brs), 6.55 (1H, d, J=6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.97 (1H, s), 7.05 (1H, dd, J=2.4, 8.8 Hz), 7.39 (1H, d, J=2.4 Hz), 7.92 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.08-8.28 (2H, m), 8.30 (1H, d, J=8.8 Hz), 9.21 (1H, s).

[0303]

The starting material was synthesized as follows.

Production example 55-1

Phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate

[0304]

The reaction similar to Production example 5-2 was performed by using N1-ethyl-5-(2-aminopyridin-4-yloxy)-1H-indole-1-carboxamide (2.9 g, 9.9 mmol, Production example 27-1), tetrahydrofuran, triethylamine and phenyl chloroformate;

the extraction and washing was performed; the obtained residue was crystallized by addition of a solvent mixture of diethyl ether: hexane = 1: 1; and the obtained crystals were filtered off, washed with diethyl ether, and dried under aeration to yield the title compound as pale pink crystals (3.7 g, 6.9 mmol, 70%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.2 Hz), 3.29 (2H, m), 6.66 (1H, d, J=3.4 Hz), 6.96 (1H, dd, J=2.0, 5.8 Hz), 7.09 (1H, dd, J=2.0, 8.0 Hz), 7.17 (4H, d, J=8.0 Hz), 7.29 (2H, d, J=8.0 Hz), 7.41-7.44 (5H, m), 7.51 (1H, d, J=2.0 Hz), 7.92 (1H, d, J=3.4 Hz), 8.22 (1H, m), 8.31 (1H, d, J=8.8 Hz), 8.42 (1H, d, J=5.8 Hz).

[0305]

Example 56

5-(2-(3-((1S)-1-Hydroxymethyl-2-oxo-2-pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide

[0306]

Similarly to Example 5, the title compound (132 mg, 0.275 mmol, 92%) was obtained as white crystals from phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate (161 mg, 0.300 mmol) synthesized in Production example 55-1 and (2S)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride (synthesized as an intermediate in Example 18).

[0307]

Example 57

5-(2-(3-((1R)-1-Hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide

[0308]

Similarly to Example 5, the title compound (127 mg, 0.257 mmol, 86%) was obtained as white crystals from phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy-carbonyl)carbamate (161 mg, 0.300 mmol) and (2R)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one (228 mg, 1.32 mmol, synthesized as an intermediate in Example 21).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.19 (3H, t, J=7.2 Hz), 1.38-1.61 (6H, m), 3.25-3.53 (8H, m), 4.75 (1H, m), 4.92 (1H, brs), 6.54 (1H, dd, J=2.4, 6.0 Hz), 6.69 (1H, d, J=3.6 Hz), 6.97 (1H, d, J=2.4 Hz), 7.05 (1H, dd, J=2.4, 9.0 Hz), 7.38 (1H, d, J=2.4 Hz), 7.92 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.08-8.27 (2H, m), 8.30 (1H, d, J=9.0 Hz), 9.21 (1H, s).

[0309]

Example 58

5-(2-(3-((1S)-1-Hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide

[0310]

Similarly to Example 5, the title compound (54.4 mg, 0.110 mmol, 73%) was obtained as white crystals from phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (80.1 mg, 0.150 mmol) synthesized in Production example 55-1 and (2S)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one hydrochloride (156 mg, 0.748 mmol, synthesized as an intermediate in Example 20).

[0311]

Example 59

5-(2-(3-(2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-oxoethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide

[0312]

The reaction similar to Example 5 was performed by using

((4-(1-ethylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)acetic acid (149 mg, 0.37 mmol) and 4-hydroxy-4-methylpiperidine monohydrochloride (68 mg, 0.45 mmol, Production example 8-3); purification was performed by silica gel column chromatography (Fuji Silysia BW-300, eluent, ethyl acetate: methanol = 9: 1; Fuji Silysia NH, eluent, ethyl acetate: methanol = 10: 1; and again Fuji Silysia BW-300, eluent, ethyl acetate-methanol system); and the obtained crystals were suspended in diethyl ether and filtered off, washed with diethyl ether and dried under

aeration to yield the title compound as colorless crystals
(40 mg, 0.081 mmol, 22%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.10 (3H, s), 1.16 (3H, t, J=7.2 Hz), 1.43 (4H, m), 3.01 (2H, m), 3.36 (2H, m), 3.89 (2H, m), 3.96 (2H, d, J=4.4 Hz), 4.37 (1H, s), 6.52 (1H, d, J=5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.91 (1H, s), 7.03 (1H, d, J=9.0 Hz), 7.37 (1H, s), 7.90 (1H, d, J=3.6 Hz), 8.03 (1H, d, J=5.6 Hz), 8.17 (1H, m), 8.22 (1H, m), 8.28 (1H, d, J=9.0 Hz), 9.27 (1H, s).

[0313]

The starting material was synthesized as follows.

Production example 59-1

((4-(1-Ethylcarbamoyl-1H-indol-5-yloxy)pyridin-2-yl)aminocarbonylamino)acetic acid

[0314]

Methyl aminoacetate hydrochloride (292 mg, 2.33 mmol) was suspended in a solvent mixture of N,N-dimethylformamide (4 ml) and triethylamine (1 ml); phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate (250 mg, 0.466 mmol, Production example 55-1) was added thereto; and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in

a solvent mixture of tetrahydrofuran (2 ml) and methanol (1 ml); and 4N aqueous solution of sodium hydroxide was added thereto while stirred at room temperature; and the reaction mixture was stirred for 1.5 hour at room temperature. After
 5 1N hydrochloric acid was added, extraction was performed with ethyl acetate-tetrahydrofuran, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crystals were suspended in diethyl ether, filtered off, washed with dimethyl ether,
 10 and dried under aeration to yield the title compound as colorless crystals (149 mg, 0.375 mmol, 80.5%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.0 Hz), 3.36 (2H, d, J=7.0 Hz), 3.81 (2H, d, J=5.2 Hz), 6.54 (1H, d, J=5.6 Hz), 6.67 (1H, d, J=3.4 Hz), 6.85 (1H, s), 7.04
 15 (1H, dd, J=2.0, 8.8 Hz), 7.37 (1H, d, J=2.0 Hz), 7.90 (1H, d, J=3.4 Hz), 8.05 (1H, d, J=5.6 Hz), 8.20-8.30 (3H, m), 9.27 (1H, s), 12.55 (1H, s).

[0315]

Example 60

20 N1-Ethyl-5-(2-(((1-methyl-4-piperidyl)methyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0316]

Similarly to Example 27, a crude product of tert-butyl 4-((((4-((1-(ethylamino)carbonyl-1H-5-indolyl)oxy)-2-pyridyl)amino)carbonyl)amino)methyl)piperidin-1-carboxyl
 25 ate was obtained from phenyl

N-(4-(1-(ethylamino)carbonyl)-1H-5-indolyl)oxy)-2-pyridyl)carbamate (150 mg, 0.36 mmol, Production example 27-2) and tert-butyl 4-aminomethyl-1-piperidine carboxylate. Trifluoroacetic acid was added to this at room temperature; the solution was stirred for 30 minutes; trifluoroacetic acid was distilled off; triethylamine-methanol was added to the residue to neutralize; and the solvent was distilled off again under reduced pressure. The residue was dissolved in tetrahydrofuran (4.0 ml)-methanol (4.0 ml); acetic acid (0.1 ml), 37% aqueous formaldehyde solution (0.5 ml) and sodium cyanoborohydride (90.5 mg, 1.44 mmol) were added at room temperature; and the reaction mixture was stirred for 1 hour. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by NH silica gel column chromatography (eluent; ethyl acetate: methanol = 98:2). The crystals were precipitated from diethyl ether, filtered off, and dried under aeration to yield the title compound as white crystals (197.0 mg, 0.44 mmol, 60.7%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.08-1.19 (5H, m), 1.30 (1H, m), 1.54 (2H, m), 1.75 (2H, m), 2.09 (3H, m), 2.70 (2H, m), 2.98 (2H, m), 3.20-3.40 (2H, m), 6.49 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.85 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=3.6 Hz), 7.90 (1H, d,

J=2.4 Hz), 8.02 (1H, d, J=5.6 Hz), 8.08 (1H, m), 8.22 (1H, m), 8.28 (1H, d, J=8.8 Hz), 9.00 (1H, s).

[0317]

Example 61

5 N1-Ethyl-5-(2-(((2-(diethylamino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0318]

Similarly to Example 27, the title compound (140.9 mg, 0.32 mmol, 89.2%) was obtained as white crystals from
10 phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl) carbamate (150 mg, 0.36 mmol, Production example 27-2) and 2-(diethylamino)ethylamine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.93 (6H, t, J=7.2 Hz),
15 1.17 (3H, t, J=7.2 Hz), 2.40-2.49 (6H, m), 3.13 (2H, m),
3.20-3.40 (2H, m), 6.49 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.82 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz),
7.36 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.00 (1H, d, J=5.6 Hz), 8.20-8.25 (2H, m), 8.28 (1H, d, J=8.8 Hz),
20 9.11 (1H, s).

[0319]

Example 62

N1-Ethyl-5-(2-(((2-(morpholin-4-yl)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

25 [0320]

Similarly to Example 27, the title compound (155.0

mg, 0.34 mmol, 95.1%) was obtained as white crystals from phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (150 mg, 0.36 mmol, Production example 27-2) and
 5 4-(2-aminoethyl)morpholine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.67 (3H, t, J=7.2 Hz), 2.30-2.40 (6H, m), 3.20 (2H, m), 3.20-3.40 (2H, m), 3.54-3.57 (4H, m), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=3.6 Hz), 7.90 (1H, d, J=2.4 Hz), 8.02 (1H, d, J=5,6 Hz), 8.10-8.25 (2H, m), 8.28 (1H, d, J=8.8 Hz), 9.11 (1H, s).

[0321]

Example 63

15 N1-Ethyl-5-(2-(((2-(4-hydroxypiperidino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0322]

Similarly to Example 27, the title compound (49.1 mg, 0.11 mmol, 35.1%) was obtained as white crystals from phenyl
 20 N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (125 mg, 0.30 mmol, Production example 27-2) and 1-(2-aminoethyl)-4-hydroxypiperidine dihydrochloride.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.2 Hz), 1.36 (2H m), 1.66-1.70 (2H, m), 2.00 (2H, m), 2.32 (2H, m), 2.65-2.69 (2H, m), 3.16 (2H, m), 3.20-3.40 (2H, m), 3.40 (1H, m), 4.53 (1H, d, J=4.0 Hz), 6.50 (1H, dd, J=2.4, 5.6

Hz), 6.67 (1H, d, J=3.6 Hz), 6.83 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.01 (1H, d, J=5.6 Hz), 8.10-8.23 (2H, m), 8.28 (1H, d, J=8.8 Hz), 9.11 (1H, s).

5 [0323]

Example 64

N1-Methyl-5-(2-(((2-(4-hydroxypiperidino)ethyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0324]

10 Similarly to Example 27, the title compound (114.3 mg, 0.25 mmol, 25.3%) was obtained as white crystals from phenyl

N-(4-(1-(methyamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (402 mg, 1.0 mmol, Production example 29-1) and
15 1-(2-aminoethyl)-4-hydroxypiperidine dihydrochloride.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.32-1.38 (2H, m), 1.60-1.70 (2H, m), 1.96-2.03 (2H, m), 2.31-2.34 (2H, m), 2.60-2.70 (2H, m), 2.83 (3H, d, J=4.4 Hz), 3.15-3.18 (2H, m), 3.42 (1H, m), 4.53 (1H, d, J=4.0 Hz), 6.51 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.04 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=2.4 Hz), 7.87 (1H, d, J=3.6 Hz), 8.01 (1H, d, J=5.6 Hz), 8.14-8.16 (2H, m), 8.28 (1H, d, J=8.8 Hz), 9.11 (1H, s).

[0325]

25 Example 65

N1-Ethyl-5-(2-((3-(diethylamino)propylamino)carbonyl)am

ino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0326]

Similarly to Example 27, the title compound (159.9 mg, 0.35 mmol, 98.1%) was obtained as white crystals from phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl) carbamate (150 mg, 0.36 mmol, Production example 27-2) and 3-(diethylamino)propylamine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.91 (6H, t, J=7.2 Hz), 1.17 (3H, t, J=7.2 Hz), 1.50 (2H, m), 2.32-2.41 (6H, m), 3.10 (2H, m), 3.20-3.40 (2H, m), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 6.81 (1H, s), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.36 (1H, d, J=3.6 Hz), 7.90 (1H, d, J=2.4 Hz), 8.00 (1H, d, J=5.6 Hz), 8.12 (1H, m), 8.22 (1H, t, J=5.2 Hz), 8.28 (1H, d, J=8.8 Hz), 9.03 (1H, s).

[0327]

Example 66N1-Ethyl-5-(2-(((3-(morpholin-4-yl)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0328]

Similarly to Example 27, the title compound (135.0 mg, 0.29 mmol, 96.4%) was obtained as white crystals from phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl) carbamate (125 mg, 0.30 mmol, Production example 27-2) and 4-(3-aminopropyl)morpholine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.2 Hz),
 1.55 (2H, m), 2.20-2.40 (6H, m), 3.11 (2H, m), 3.20-3.40
 (2H, m), 3.51-3.55 (4H, m), 6.50 (1H, dd, J=2.4, 5.6 Hz),
 6.67 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.03 (1H, dd, J=2.4,
 5 8.8 Hz), 7.36 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz),
 8.01 (1H, d, J=5.6 Hz), 8.04 (1H, m), 8.21 (1H, t, J=5.6
 Hz), 8.28 (1H, d, J=8.8 Hz), 9.02 (1H, s).

[0329]

Example 67

10 N1-Ethyl-5-(2-(((3-(4-methylpiperazino)propyl)amino)car
 bonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0330]

Similarly to Example 27, the title compound (141.9
 mg, 0.30 mmol, 98.6%) was obtained as white crystals from
 15 phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl
)carbamate (125 mg, 0.30 mmol, Production example 27-2) and
 1-(3-aminopropyl)-4-methylpiperazine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.2 Hz),
 20 1.54 (2H, m), 2.11 (3H, s), 2.11-2.40 (10H, m), 3.08 (2H,
 m), 3.20-3.40 (2H, m), 6.50 (1H, dd, J=2.4, 5.6 Hz), 6.67
 (1H, d, J=3.6 Hz), 6.84 (1H, s), 7.03 (1H, dd, J=2.4, 8.8
 Hz), 7.36 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.01
 (1H, d, J=5.6 Hz), 8.04 (1H, m), 8.22 (1H, t, J=5.6 Hz),
 25 8.28 (1H, d, J=8.8 Hz), 9.01 (1H, s).

[0331]

Example 68

N1-Cyclopropyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

5 [0332]

Tetrahydrofuran (30 ml) and triethylamine (3.87 ml, 27.8 mmol) were added to N1-cyclopropyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (2.85 g, 9.25 mmol, CAS No. 417722-12-4) which was described in WO 02/32872; phenyl chloroformate (2.57 ml, 20.4 mmol) was added thereto at 0 °C while stirred; and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated to yield 15 3.30 g of the mixture of phenyl N-(4-(1-(cyclopropylamino)carbonyl-1H-5-indolyl)-oxy-2-pyridyl)carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxy carbonyl)carbamate. A portion of 0.524 g of the mixture was dissolved in N,N-dimethylformamide (5 ml); 4-(1-pyrrolidinyl)piperidine (0.736 g, 4.80 mmol) was added thereto; the reaction mixture was stirred for 5 hours; the reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated to yield 20 the title compound as white crystals (280 mg, 0.57 mmol). MS Spectrum (ESI): 489 (M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.57-0.75 (4H, m),
 1.18-1.30 (2H, m), 1.58-1.80 (6H, m), 2.03-2.12 (1H, m),
 2.38-2.48 (4H, m), 2.72-2.87 (3H, m), 3.88-3.96 (2H, m),
 6.53 (1H, dd, J=2.7, 6.1 Hz), 6.64 (1H, d, J=3.4 Hz), 7.03
 5 (1H, dd, J=2.7, 8.9 Hz), 7.30 (1H, d, J=2.7 Hz), 7.35 (1H,
 d, J=2.7 Hz), 7.86 (1H, d, J=3.4 Hz), 8.06 (1H, d, J=6.1
 Hz), 8.24-8.29 (2H, m), 9.08 (1H, s).

[0333]

Example 69

10 5-(2-(3-((1R)-1-Hydroxymethyl-2-oxo-2-pyrrolidin-1-yl)et
 hyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid
 cyclopropylamide

[0334]

Similarly to Example 5, the title compound (113 mg,
 15 0.229 mmol) was obtained as white crystals from a mixture
 (165 mg) of
 N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyr
 idyl)-N-(phenoxycarbonyl)carbamate and phenyl
 N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyr
 20 idyl)carbamate, intermediates in Example 68, and
 (2R)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one
 (265 mg, 1.67 mmol, synthesized as an intermediate in Example
 55).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.66 (2H, m),
 25 0.70-0.78 (2H, m), 1.72-1.90 (4H, m), 2.78 (1H, m), 3.20-3.60
 (6H, m), 4.54 (1H, m), 4.98 (1H, t, J=5.6 Hz), 6.53 (1H,

dd, J=2.0, 6.0 Hz), 6.67 (1H, d, J=3.6 Hz) 6.97 (1H, d, J=2.0 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.37 (1H, d, J=2.4 Hz), 7.88 (1H, d, J= 3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.16 (1H, brs), 8.25-8.34 (2H, m), 9.18 (1H, s).

5 [0335]

Example 70

5-(2-(3-((1S)-1-Hydroxymethyl-2-oxo-2-pyrrolidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide

10 [0336]

Similarly to Example 5, the title compound (117 mg, 0.237 mmol) was obtained as white crystals from a mixture (165 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)carbamate, intermediates in Example 68, and (2S)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)propan-1-one hydrochloride (synthesized as an intermediate in Example 18).

20

[0337]

Example 71

5-(2-(3-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide

25 [0338]

Similarly to Example 5, the title compound (90.9 mg,

0.197 mmol) was obtained as white crystals from a mixture
 (165 mg) of phenyl
 N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyr
 idyl)-N-(phenoxycarbonyl) carbamate and phenyl
 5 N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyr
 idyl) carbamate, intermediates in Example 68, and
 2-amino-1-(pyrrolidin-1-yl)ethanone hydrochloride (247 mg,
 1.50 mmol, synthesized as an intermediate in Example 7).
¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.66 (2H, m),
 10 0.71-0.79 (2H, m), 1.72-1.80 (2H, m), 1.83-1.91 (2H, m),
 2.78 (1H, m), 3.28-3.40 (4H, m), 3.89 (2H, d, J=4.4 Hz),
 6.54 (1H, dd, J=2.0, 6.0 Hz), 6.67 (1H, d, J=3.6 Hz), 6.94
 (1H, d, J=2.0 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.38 (1H,
 d, J=2.4 Hz), 7.88 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0
 15 Hz), 8.17 (1H, brs), 8.26-8.35 (2H, m), 9.28 (1H, s).

[0339]

Example 72

5-(2-(3-(3-Oxo-3-(pyrrolidin-1-yl)propyl)ureido)pyridin
 -4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide

[0340]

Similarly to Example 5, the title compound (113 mg,
 0.237 mmol) was obtained as white crystals from a mixture
 (165 mg) of phenyl
 N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyr
 25 idyl)-N-(phenoxycarbonyl) carbamate and phenyl
 N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyr

idyl)carbamate, intermediates in Example 68, and 3-amino-1-(pyrrolidin-1-yl)propan-1-one hydrochloride (268 mg, 1.50 mmol, synthesized as an intermediate in Example 25).

5 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.66 (2H, m), 0.71-0.79 (2H, m), 1.70-1.79 (2H, m), 1.79-1.88 (2H, m), 2.40 (2H, t, J=6.4 Hz), 2.78 (1H, m), 3.24-3.38 (6H, m), 6.51 (1H, dd, J=2.0, 6.0 Hz), 6.67 (1H, d, J=3.8 Hz), 6.93 (1H, d, J=2.0 Hz), 7.05 (1H, dd, J=2.4, 8.8 Hz), 7.37 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=3.8 Hz), 7.98-8.10 (2H, m), 8.26-8.34 (2H, m), 9.09 (1H, s).

[0341]

Example 73

15 5-(2-(3-((1R)-1-Hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide

[0342]

Similarly to Example 5, the title compound (106 mg, 0.209 mmol) was obtained as white crystals from a mixture (165 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)carbamate, intermediates in Example 68, and (2R)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one (228 mg, 1.32 mmol, synthesized as an intermediate in Example

57).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.66 (2H, m), 0.70-0.78 (2H, m), 1.38-1.62 (6H, m), 2.79 (1H, m), 3.38-3.53 (6H, m), 4.75 (1H, m), 4.93 (1H, t, J=5.8 Hz), 6.54 (1H, dd, J=2.0, 6.0 Hz), 6.67 (1H, d, J=3.6 Hz), 6.97 (1H, d, J=2.0 Hz), 7.06 (1H, dd, J=2.4, 8.8 Hz), 7.37 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=3.6 Hz), 8.05 (1H, d, J=6.0 Hz), 8.10-8.34 (3H, m), 9.20 (1H, s).

[0343]

10 Example 74

5-(2-(3-((1S)-1-Hydroxymethyl-2-oxo-2-piperidin-1-ylethyl)ureido)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopropylamide

[0344]

15 Similarly to Example 5, the title compound (66.8 mg, 0.132 mmol) was obtained as white crystals from a mixture (82.3 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl) carbamate, intermediates in Example 68, and (2S)-2-amino-3-hydroxy-1-(piperidin-1-yl)propan-1-one hydrochloride (156 mg, 0.748 mmol, synthesized as an intermediate in Example 20).

25 [0345]

Example 75

N1-Phenyl-5-(2-(((3-(diethylamino)propyl)amino)carbonyl
)amino-4-pyridyl)-oxy-1H-1-indolecarboxamide

[0346]

The title compound was obtained from
5 N1-phenyl-5-(2-amino-4-pyridyl)oxy)-1H-1-indolecarboxam
ide (CAS No. 417721-87-0) which was written in the
description of WO 02/32872 and 3-diethylaminopropylamine
using a procedure analogous to that described for Example
28.

10 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.91 (6H, t, J=7.2 Hz),
1.47-1.53 (2H, m), 2.30-2.44 (6H, m), 3.05-3.14 (2H, m),
6.52 (1H, dd, J=6.0, 2.0 Hz), 6.76 (1H, d, J=3.6 Hz), 6.84
(1H, d, J=2.0 H), 7.09 (1H, dd, J=9.2, 2.4 Hz), 7.13 (1H,
t, J=7.6 Hz), 7.38 (2H, dd, J=7.6, 7.6 Hz), 7.42 (1H, d,
15 J=2.4 Hz), 7.64 (2H, d, J=7.6 Hz), 8.02 (1H, d, J=6.0 Hz),
8.10-8.14 (2H, m), 8.27 (1H, d, J=9.2 Hz), 9.05 (1H, brs),
10.10 (1H, brs).

[0347]

Example 76

20 N1-Phenyl-5-(2-(((3-(4-methylpiperazin-1-yl)propyl)amin
o)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0348]

Similarly to Example 28, the title compound was
obtained from
25 N1-phenyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxami
de (CAS No. 417721-87-0) which was described in WO 02/32872

and 1-(3-aminopropyl)-4-methylpiperazine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.52-1.59 (2H, m), 2.13 (3H, s), 2.15-2.45 (10H, m), 3.08-3.15 (2H, m), 6.54 (1H, dd, J=6.0, 2.0 Hz), 6.79 (1H, d, J=3.6 Hz), 6.89 (1H, brs), 7.10 (1H, dd, J=2.4, 9.2 Hz), 7.15 (1H, t, J=7.6 Hz), 7.40 (2H, t, J=7.6 Hz), 7.44 (1H, d, J=2.4 Hz), 7.66 (2H, d, J=7.6 Hz), 8.03-8.07 (2H, m), 8.14 (1H, d, J=3.6 Hz), 8.29 (1H, d, J=9.2 Hz), 9.05 (1H, brs), 10.10 (1H, brs).

[0349]

10 Example 77

N1-Ethyl-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0350]

Tetrahydrofuran (20 ml) and triethylamine (2.70 ml, 19.4 mmol) were added to N1-ethyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide (1.91 g, 6.45 mmol, Production example 27-1); phenyl chloroformate (1.79 ml, 14.2 mmol) was added thereto at 0 °C while stirred; and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated to yield a mixture (2.95 g) of phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate. A portion of 0.454 g of

the mixture was dissolved in N,N-dimethylformamide (5 ml);
 and 4-tetrahydro-1H-1-pyrrolylpiperidine (0.522 g, 3.39
 mmol) was added; and the reaction mixture was stirred for
 5 hours. The reaction mixture was partitioned between ethyl
 acetate and water; the organic layer was concentrated to
 yield a solid; the obtained solid was washed with hexane:
 diethyl ether=1: 1 to yield the title compound as crystals
 (205 mg, 0.43 mmol).

MS Spectrum (ESI): 477 (M+1), 953 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.12-1.22 (5H, m),
 1.57-1.81 (6H, m), 2.05-2.15 (1H, m), 2.38-2.50 (4H, m),
 2.77-2.78 (2H, m), 3.28-3.37 (2H, m), 3.87-3.97 (2H, m),
 6.53 (1H, dd, J=2.5, 5.4 Hz), 6.66 (1H, d, J=3.5 Hz), 7.02
 (1H, dd, J=2.5, 8.9 Hz), 7.30 (1H, d, J=2.5 Hz), 7.36 (1H,
 d, J=2.5 Hz), 7.89 (1H, d, J=3.5 Hz), 8.05 (1H, d, J=5.4
 Hz), 8.20 (1H, m), 8.27 (1H, t, J=8.9 Hz), 9.08 (1H, s).

[0351]

Example 78

5-(2-(((4-Hydroxy-4-methylpiperidin-1-yl)carbonyl)amino
)pyridin-4-yloxy)-1H-indole-1-carboxylic acid ethylamide

[0352]

Similarly to Example 41, the title compound was
 obtained as colorless crystals (124 mg, 0.283 mmol, 89.4%)
 from 4-hydroxy-4-methylpiperidine monohydrochloride (216
 mg, 1.42 mmol, Production example 8-3) and phenyl
 N-(4-(1-(ethylaminocarbonyl-1H-indol-5-yloxy)-pyridin-2

-yl)-N-(phenoxycarbonyl)carbamate (170 mg, 0.317 mmol, Production example 55-1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.08 (3H, s), 1.17 (3H, t, J=7.2 Hz), 1.38-1.44 (4H, m), 3.13 (2H, m), 3.30 (2H, m), 3.63 (2H, m), 4.27 (1H, s), 6.53 (1H, dd, J=2.4, 6.0 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.32 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.0 Hz), 8.05 (1H, d, J=6.0 Hz), 8.21 (1H, t, J=5.4 Hz), 8.27 (1H, d, J=8.8 Hz), 9.04 (1H, s).

[0353]

Example 79

N1-Ethyl-5-(2-((4-hydroxypiperidin-1-yl)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0354]

Similarly to Example 27, the title compound was obtained as white powder (18.7 mg, 0.044 mmol, 14.7%) from phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate (125 mg, 0.30 mmol, Production example 27-2) and 4-hydroxypiperidine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.13-1.27 (5H, m), 1.63-1.67 (2H, m), 2.98 (2H, m), 3.20-3.40 (2H, m), 3.60 (1H, m), 3.74 (2H, m), 4.64 (1H, d, J=4.4 Hz), 6.53 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.31 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.6 Hz), 8.21

(1H, t, J=5.2 Hz), 8.27 (1H, d, J=8.8 Hz), 9.09 (1H, s).

[0355]

Example 80

N1-Ethyl-5-(2-(piperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0356]

N,N-Dimethylformamide (4 ml) and piperidine (0.31 ml, 3.13 mmol) were added to a mixture (0.336 g) of phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate obtained in Example 77; the reaction mixture was stirred overnight; the reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated to yield the title compound as crystals (182 mg, 0.45 mmol).

MS Spectrum (ESI): 408 (M+1), 815 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.18 (3H, t, J=7.6 Hz), 1.35-1.57 (6H, m), 3.23-3.33 (6H, m), 6.52 (1H, dd, J=2.4, 5.4 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, dd, J=2.4, 8.7 Hz), 7.30 (1H, d, J=2.4 Hz), 7.36 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.4 Hz), 8.06 (1H, d, J=5.5 Hz), 8.21 (1H, t, J=5.5 Hz), 8.27 (1H, d, J=8.7 Hz), 9.05 (1H, s).

[0357]

Example 81

N1-Ethyl-5-((2-((pyrrolidin-1-ylcarbonyl)amino)-4-pyridyl)oxy-1H-1-indolecarboxamide

yl)oxy)-1H-1-indolecarboxamide

[0358]

N,N-Dimethylformamide (5 ml) and pyrrolidine (0.36 ml, 4.3 mmol) were added to a mixture (0.461 g) of phenyl N-(4-(1-(ethylamino)carbonyl)-1H-5-indolyl)oxy-2-pyridyl carbamate and phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy)-2-pyridyl)-N-(phenoxy carbonyl)carbamate obtained in Example 77; the reaction mixture was stirred overnight; the reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated to yield the title compound as crystals (245 mg, 0.623 mmol).

MS Spectrum (ESI): 394 (M+1), 787 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.16 (3H, t, J=7.6 Hz), 1.70-1.82 (4H, m), 3.22-3.40 (6H, m), 6.54 (1H, dd, J=2.4, 5.5 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, dd, J=2.4, 8.7 Hz), 7.35 (1H, d, J=2.4 Hz), 7.41 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.4 Hz), 8.06 (1H, d, J= 5.5 Hz), 8.21 (1H, t, J=5.5 Hz), 8.27 (1H, d, J=8.7 Hz), 8.59 (1H, s).

[0359]

Example 82

N4-(4-((1-(Ethylamino)carbonyl-1H-5-indolyl)oxy)-2-pyridyl)-4-morpholinecarboxamide

[0360]

N,N-Dimethylformamide (5 ml) and morpholine (0.326 ml, 3.73 mmol) were added to a mixture (0.401 g) of phenyl

N-(4-(1-(ethylamino)carbonyl)-1H-5-indolyl)oxy-2-pyridyl carbamate and phenyl N-(4-(1-(ethylamino)carbonyl-1H-5-indolyl)oxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate obtained in Example 77; the reaction mixture was stirred overnight; the reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; and the obtained solid was washed with a solvent mixture of hexane: diethyl ether = 1: 1 to yield the title compound (255 mg, 0.62 mmol).

MS Spectrum (ESI): 410 (M+1), 819 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.7 Hz), 3.25-3.42 (6H, m), 3.48-3.53 (4H, m), 6.55 (1H, dd, J=2.6, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.02 (1H, dd, J=2.6, 8.7 Hz), 7.29 (1H, d, J=2.6 Hz), 7.35 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.08 (1H, d, J=5.6 Hz), 8.20 (1H, t, J=5.6 Hz), 8.28 (1H, t, J=5.6 Hz), 9.19 (1H, s).

[0361]

Example 83

N1-Ethyl-5-(2-((1,1-dioxothiomorpholin-4-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0362]

Similarly to Example 54, the title compound was obtained as colorless crystals (116 mg, 0.253 mmol, 80.0%) from 1,1-dioxothiomorpholine hydrochloride (248 mg, 1.42 mmol, Production example 54-3) and phenyl N-(4-(1-(ethylamino)carbonyl-1H-indol-5-yloxy)-pyridin-

2-yl)-N-(phenoxycarbonyl)carbamate (170 mg, 0.317 mmol, Production example 55-1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.2 Hz), 3.10 (4H, m), 3.29 (2H, m), 3.80 (4H, m), 6.58 (1H, dd, J=2.0, 5.6 Hz), 6.67 (1H, d, J=3.4 Hz), 7.03 (1H, dd, J=2.0, 9.0 Hz), 7.31 (1H, d, J=2.0 Hz), 7.36 (1H, d, J=2.0 Hz), 7.90 (1H, d, J=3.4 Hz), 8.10 (1H, d, J=5.6 Hz), 8.22 (1H, t, J=5.4 Hz), 8.28 (1H, d, J=9.0 Hz), 9.54 (1H, s).

[0363]

10 Example 84

N1-Ethyl-5-(2-((methoxylamino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0364]

15 Similarly to Example 27, the title compound was obtained as white crystals (94.3 mg, 0.26 mmol, 70.9%) from phenyl

N-(4-(1-(ethylamino)carbonyl-1H-5-indolylyl)oxy-2-pyridinyl)carbamate (150 mg, 0.36 mmol, Production example 27-2) and methoxylamine hydrochloride.

20 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17 (3H, t, J=7.2 Hz), 3.20-3.40 (2H, m), 3.59 (3H, s), 6.57 (1H, dd, J=2.4, 5.6 Hz), 6.67 (1H, d, J=3.6 Hz), 7.05 (1H, dd, J=2.4, 8.8 Hz), 7.16 (1H, s), 7.38 (1H, d, J=2.4 Hz), 7.90 (1H, d, J=3.6 Hz), 8.08 (1H, d, J=5.6 Hz), 8.21 (1H, m), 8.28 (1H, d, J=8.8 Hz), 8.95 (1H, s), 10.15 (1H, s).

25 [0365]

Example 85

N1-Cyclopropyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0366]

5 N,N-Dimethylformamide (5ml) and 4-hydroxypiperidine (433 mg, 4.29 mmol) were added to a mixture (470 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxy-carbonyl)carbamate obtained in Example 68; the reaction mixture was stirred overnight; the reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated to yield the title compound as white crystals (220 mg, 0.51 mmol, 39%).

15 MS Spectrum (ESI): 436 (M+1), 871 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.63 (2H, m), 0.69-0.76 (2H, m), 1.18-1.30 (2H, m), 1.60-1.70 (2H, m), 2.70-2.80 (1H, m), 2.93-3.02 (2H, m), 3.55-3.64 (1H, m), 3.69-3.77 (2H, m), 4.63 (1H, d, J=4.4 Hz), 6.53 (1H, dd, J=2.4, 5.8 Hz), 6.64 (1H, d, J=3.6 Hz), 7.04 (1H, dd, J=2.4, 8.5 Hz), 7.31 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.86 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.8 Hz), 8.24-8.29 (2H, m), 9.08 (1H, s).

[0367]

25 Example 86

N1-Cyclopropyl-5-(2-(((4-hydroxy-4-methylpiperidin-1-yl

)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0368]

Similarly to Example 41, the title compound was obtained as colorless crystals (109 mg, 0.242 mmol) from 4-hydroxy-4-methylpiperidine monohydrochloride (221 mg, 1.46 mmol, Production example 8-3) and a mixture (200 mg, intermediates in Example 68) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyloxy)-2-pyridyl)carbamate.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.61 (2H, m), 0.73 (2H, m), 1.08 (3H, s), 1.30-1.41 (4H, m), 2.76 (1H, m), 3.14 (2H, m), 3.63 (2H, m), 4.27 (1H, s), 6.53 (1H, d, J=5.4 Hz), 6.65 (1H, d, J=3.4 Hz), 7.03 (1H, d, J=8.8 Hz), 7.32 (1H, s), 7.35 (1H, s), 7.86 (1H, d, J=3.4 Hz), 8.06 (1H, d, J=5.4 Hz), 8.27 (2H, m), 9.04 (1H, s).

[0369]

Example 87

N4-(4-(1-(Cyclopropylamino)carbonyl)-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide

[0370]

N,N-Dimethylformamide (5 ml) and morpholine (0.373 ml, 4.28 mmol) were added to a mixture (470 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl

N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate obtained in Example 68; and the reaction mixture was stirred overnight; the reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; and the obtained solid was washed with a solvent mixture of hexane: diethyl ether = 1: 1 to yield the title compound (255 mg, 0.58 mmol, 95%). MS Spectrum (ESI): 422 (M+1), 843 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.75 (4H, m), 2.72-2.81 (1H, m), 3.26-3.40 (4H, m), 3.50 (4H, t, J=4.8 Hz), 6.56 (1H, dd, J=2.5, 5.6 Hz), 6.65 (1H, d, J=3.4 Hz), 7.04 (1H, dd, J=2.5, 8.8 Hz), 7.30 (1H, d, J=2.5 Hz), 7.36 (1H, d, J=2.5 Hz), 7.86 (1H, d, J=3.4 Hz), 8.08 (1H, d, J=5.5 Hz), 8.24-8.30 (2H, m), 9.18 (1H, s).

[0371]

Example 88

N1-Cyclopropyl-5-(2-((pyrrolidin-1-ylcarbonyl)amino)-4-pyridyl)oxy-1H-1-indolecarboxamide

[0372]

N,N-Dimethylformamide (5 ml) and pyrrolidine (0.35 ml, 4.2 mmol) were added to a mixture (470 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate obtained in Example 68; the reaction mixture was stirred overnight; the reaction

mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated to yield the title compound as white crystals (200 mg, 0.49 mmol).

MS Spectrum (ESI): 406 (M+1), 811 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.78 (4H, m), 1.70-1.83 (4H, m), 2.73-2.81 (1H, m), 3.23-3.45 (4H, m), 6.55 (1H, dd, J=2.2, 5.7 Hz), 6.65 (1H, d, J=3.5 Hz), 7.03 (1H, dd, J=2.2, 8.7 Hz), 7.36 (1H, d, J=2.2 Hz), 7.41 (1H, d, J=2.2 Hz), 7.86 (1H, d, J=3.5 Hz), 8.06 (1H, d, J=5.7 Hz), 8.16-8.30 (2H, m), 8.59 (1H, s).

[0373]

Example 89

N1-Cyclopropyl-5-(2-(piperidin-1-ylcarbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0374]

N,N-Dimethylformamide (5 ml) and piperidine (0.42 ml, 4.2 mmol) were added to a mixture (467 mg) of phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-cyclopropylaminocarbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxy-carbonyl)carbamate obtained in Example 68; and the reaction mixture was stirred overnight; the reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; the obtained solid was washed with a solvent mixture of hexane: diethyl ether = 1: 1 to yield the title compound as crystals (241 mg, 0.57

mmol).

MS Spectrum (ESI): 420 (M+1), 839 (2M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.58-0.77 (4H, m),
1.34-1.55 (6H, m), 2.72-2.81 (1H, m), 3.27-3.40 (4H, m),
5 6.52 (1H, dd, J=2.6, 5.6 Hz), 6.64 (1H, d, J=3.6 Hz), 7.03
(1H, dd, J=2.6, 8.7 Hz), 7.30 (1H, d, J=2.6 Hz), 7.35 (1H,
d, J=2.6 Hz), 7.87 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.6
Hz), 8.23-8.30 (2H, m), 9.03 (1H, s).

[0375]

10 Example 90

N4-(4-(1-(Cyclopentylamino)carbonyl-1H-5-indolyl)oxy-2-
pyridyl)-4-morpholinecarboxamide

[0376]

Phenyl

15 N-(4-(1-cyclopentylaminocarbonyl-1H-indol-5-yloxy)-2-py
ridyl)-N-(phenoxycarbonyl)carbamate (200 mg, 0.35 mmol)
was dissolved in N,N-dimethylformamide (1.5 ml) and
morpholine (0.15 ml, 1.73 mmol); and the reaction mixture
was stirred at room temperature overnight. The reaction
20 mixture was partitioned between ethyl acetate and water;
and the organic layer was washed with brine, dried over
anhydrous magnesium sulfate, and concentrated under reduced
pressure. The residue was purified by silica gel column
chromatography (Fuji Silysia BW-300; ethyl acetate, ethyl
25 acetate: methanol = 10: 1 in this order); the obtained
colorless oil was crystallized by addition of diethyl ether;

and the crystals were filtered off, washed with diethyl ether, and dried under aeration to yield the title compound as colorless crystals (140 mg, 0.31 mmol, 90%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.48-1.64 (4H, m), 1.66-1.76 (2H, m), 1.88-1.98 (2H, m), 3.35 (4H, m), 3.51 (4H, m), 4.14 (1H, m), 6.56 (1H, d, J=6.0 Hz), 6.65 (1H, d, J=3.6 Hz), 7.02 (1H, d, J=8.8 Hz), 7.30 (1H, s), 7.35 (1H, s), 7.96 (1H, d, J=3.6 Hz), 8.00 (1H, d, J=6.8 Hz), 8.08 (1H, d, J=6.0 Hz), 8.25 (1H, d, J=8.8 Hz), 9.18 (1H, s).

[0377]

The starting materials were synthesized as follows.

Production example 90-1

Phenyl N-cyclopentylcarbamate

[0378]

Cyclopentylamine (9.9 ml, 100 mmol) was dissolved in tetrahydrofuran (400 ml); pyridine (8.9 ml, 110 mmol) was added thereto; and the reaction mixture was stirred. The reaction mixture was cooled with ice; phenyl chloroformate (13.8 ml, 110 mmol) was added dropwise for 5 minutes while stirring; and the reaction mixture was stirred at room temperature for 24.5 hours. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crystals were suspended in a solvent mixture of

hexane: ethyl acetate = 5: 1, filtered off, washed with hexane, and dried under aeration to yield the title compound as colorless crystals (16.6 g, 81 mmol, 81%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.47 (4H, m), 1.63 (2H, m), 1.81 (2H, m), 3.81 (1H, m), 7.07 (2H, d, J=7.6 Hz), 7.17 (1H, t, J=7.6 Hz), 7.35 (2H, t, J=7.6 Hz), 7.75 (1H, d, J=6.8 Hz).

[0379]

Production example 90-2

N1-Cyclopentyl-5-(2-aminopyridin-4-yloxy)-1H-1-indolecarboxamide

[0380]

4-(1H-5-Indolyloxy)-2-pyridinamine (2.50 g, 11.1 mmol, CAS No. 417722-11-3), which was described in WO 02/32872, was dissolved in N,N-dimethylformamide (30 ml); sodium hydride (0.530 g, 13.3 mmol) was added thereto at room temperature; and the reaction mixture was stirred for 30 minutes. Phenyl N-cyclopentylcarbamate (2.50 g, 12.2 mmol) was added thereto at room temperature while stirring; and the reaction mixture was stirred for 30 minutes. Water was added to the reaction mixture; and the precipitated crystals were filtered off, and washed with water. This crystals were dissolved in methanol, and purified by silica gel column chromatography (Fuji Silysia NH; hexane: ethyl acetate = 1: 1, ethyl acetate, ethyl acetate: methanol = 98: 2 in this order). The obtained crystals were suspended

in hexane: ethanol = 10: 1, filtered off, washed with hexane, and dried under aeration to yield the title compound as colorless crystals (2.08 g, 6.18 mmol, 55.7%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.56 (4H, m), 1.71 (2H, m), 1.92 (2H, m), 4.14 (1H, m), 5.74 (1H, d, J=2.0 Hz), 5.83 (2H, s), 6.12 (1H, dd, J=2.0, 5.6 Hz), 6.64 (1H, d, J=3.4 Hz), 7.00 (1H, dd, J=2.0, 8.8 Hz), 7.32 (1H, d, J=2.0 Hz), 7.75 (1H, d, J=5.6 Hz), 7.94 (1H, d, J=3.4 Hz), 7.97 (1H, d, J=6.4 Hz), 8.23 (1H, d, J=8.8 Hz).

[0381]

Production example 90-3

Phenyl

N-(4-(1-cyclopentylaminocarbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxycarbonyl) carbamate

[0382]

N1-Cyclopentyl-5-(2-aminopyridin-4-yloxy)-1H-1-indolecarboxamide (1.55 g, 4.58 mmol) was dissolved in tetrahydrofuran (90ml); triethylamine (1.43ml, 10.31mmol) and pyridine (0.56 ml, 6.88 mmol) were added thereto; and the reaction mixture was stirred. The reaction mixture was cooled with ice; phenyl chloroformate (1.44 ml, 11.45 mmol) was added dropwise; and the reaction mixture was stirred at room temperature for 2.5 hours. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (Fuji Silysia BW-300; hexane: ethyl acetate = 1: 1, 1: 3 in this order) to yield the title compound as a colorless amorphous solid (2.516 g, 4.36 mmol, 95.2%).

5 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.50-1.63 (4H, m), 1.66-1.74 (2H, m), 1.88-1.98 (2H, m), 4.15 (1H, m), 6.65 (1H, d, J=3.8 Hz), 6.95 (1H, dd, J=2.4, 5.6 Hz), 7.09 (1H, dd, J=2.4, 8.8 Hz), 7.16 (4H, d, J=7.6 Hz), 7.29 (2H, d, J=7.6 Hz), 7.42 (4H, d, J=7.6 Hz), 7.44 (1H, d, J=2.4 Hz), 7.51 (1H, d, J=2.4 Hz), 7.98 (1H, d, J=3.8 Hz), 8.01 (1H, d, J=6.8 Hz), 8.28 (1H, d, J=8.8 Hz), 8.42 (1H, d, J=5.6 Hz).

[0383]

Example 91

15 5-(2-(((4-Hydroxypiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-indole-1-carboxylic acid cyclopentylamide

[0384]

Similarly to Example 90, the title compound was obtained as colorless crystals (129 mg, 0.278 mmol, 80.2%) from phenyl N-(4-(1-cyclopentylaminocarbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxy carbonyl) carbamate (200 mg, 0.346 mmol, Production example 90-3) and 4-hydroxypiperidine (175 mg, 1.73 mmol).

25 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.23 (2H, m), 1.48-1.77 (8H, m), 1.92 (2H, m), 2.98 (2H, m), 3.59 (1H, m), 3.73 (2H,

m), 4.15 (1H, m), 4.64 (1H, d, J=4.4 Hz), 6.53 (1H, dd, J=2.0, 5.6 Hz), 6.65 (1H, d, J=3.6 Hz), 7.02 (1H, dd, J=2.0, 9.0 Hz), 7.31 (1H, d, J=2.0 Hz), 7.35 (1H, d, J=2.0 Hz), 7.96 (1H, d, J=3.6 Hz), 7.99 (1H, d, J=6.8 Hz), 8.06 (1H, d, J=5.6 Hz), 8.24 (1H, d, J=9.0 Hz), 9.09 (1H, s).

[0385]

Example 92

N1-Cyclopentyl-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0386]

Similarly to Example 90, the title compound was obtained as colorless crystals (83 mg, 0.161 mmol, 46.3%) from phenyl N-(4-(1-cyclopentylaminocarbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (200 mg, 0.346 mmol, Production example 90-3) and 4-(1-pyrrolidinyl)piperidine (268 mg, 1.73 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.18-1.30 (2H, m), 1.50-1.80 (12H, m), 1.87-1.98 (2H, m), 2.08 (1H, m), 2.43 (4H, m), 2.81 (2H, m), 3.91 (2H, m), 4.15 (1H, m), 6.53 (1H, dd, J=2.0, 5.6 Hz), 6.65 (1H, d, J=3.6 Hz), 7.02 (1H, dd, J=2.0, 9.0 Hz), 7.31 (1H, d, J=2.0 Hz), 7.35 (1H, d, J=2.0 Hz), 7.96 (1H, d, J=3.6 Hz), 7.99 (1H, d, J=6.8 Hz), 8.06 (1H, d, J=5.6 Hz), 8.25 (1H, d, J=9.0 Hz), 9.08 (1H, s).

[0387]

Example 93

N1-(3-Methylbutyl)-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0388]

5 N,N-dimethylformamide (30 ml), pyridine (0.52 ml, 6.4 mmol) and triethylamine (1.35 ml, 9.69 mmol) were added to N1-(3-methylbutyl)-5-((2-amino-4-pyridyl)oxy)-1H-1-indolecarboxamide (1.45 g, 4.29 mmol); phenyl chloroformate (0.81 ml, 6.4 mmol) was added at 0 °C while stirring; and
10 the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated and subjected to silica gel column chromatography to yield a mixture (2.0 g) of phenyl
15 N-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate. A portion of 0.4 g of the mixture was dissolved in N,N-dimethylformamide
20 (4 ml); 4-tetrahydro-1H-1-pyrrolylpiperidine (0.43 g, 2.8 mmol) was added thereto; and the reaction mixture was stirred for 2 hours. The reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; and the residue was purified by silica gel column
25 chromatography (Fuji Silysia NH, ethyl acetate: methanol = 10: 1) to yield the title compound as white crystals (275

mg, 0.53 mmol).

MS Spectrum (ESI): 519(M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.91 (6H, d, J=7.6 Hz),
1.18-1.30 (3H, m), 1.47 (2H, q, J=7.6 Hz), 1.57-1.80 (6H,
5 m), 2.03-2.22 (1H, m), 2.37-2.48 (4H, m), 2.76-2.85 (2H,
m), 3.25-3.36 (2H, m), 3.88-3.97 (2H, m), 6.53 (1H, dd, J=2.4,
5.4 Hz), 6.66 (1H, d, J=3.6 Hz), 7.02 (1H, dd, J=2.4, 8.7
Hz), 7.31 (1H, d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.90
(1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.4 Hz), 8.16 (1H, t, J=5.4
10 Hz), 8.27 (1H, d, J=8.7 Hz), 9.08 (1H, s).

[0389]

The starting materials were synthesized as follows.

Production example 93-1

N1-(3-Methylbutyl)-5-((2-amino-4-pyridyl)oxy)-1H-1-indo
15 lecarboxamide

[0390]

4-(1H-5-Indolyloxy)-2-pyridinamine (2.0 g, 8.9 mmol,
CAS No. 417722-11-3) which was described in WO 02/32872 was
dissolved in N,N-dimethylformamide (20 ml); and sodium
20 hydride (426 mg, 10.7 mmol) was added thereto at room
temperature while stirring. The reaction mixture was
cooled with ice bath after 30 minutes; phenyl
N-(3-methylbutyl)carbamate (2.02 g, 9.75 mmol) was added
thereto; and the reaction mixture was stirred for 3 hours
25 at room temperature. The reaction mixture was partitioned
between ethyl acetate and water; the organic layer was washed

with water and brine, dried over anhydrous sodium sulfate, and concentrated; and the residue was purified by NH-silica gel column chromatography (hexane: ethyl acetate = 3:1) to yield the title compound as crystals (1.45 g, 4.3 mmol, 48%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.89-0.93 (6H, m), 1.40-1.70 (3H, m), 3.25-3.40 (2H, m), 5.72-5.75 (1H, m), 5.83 (2H, s), 6.10-6.40 (1H, m), 6.64-6.68 (1H, m), 6.98-7.02 (1H, m), 7.30-7.34 (1H, m), 7.75 (1H, dd, J=1.5, 6.0 Hz), 7.86-7.90 (1H, m), 8.14 (1H, t, J=4.5 Hz), 8.25 (1H, d, J=9.0 Hz).

[0391]

Production example 93-2

Phenyl N-(3-methylbutyl)carbamate

[0392]

Phenyl chloroformate (14.8 ml, 0.117 mol) was dissolved in tetrahydrofuran (200 ml); triethylamine (18.0 ml, 0.129 mol) and isoamylamine (15.0 ml, 0.129 mol) were added thereto at room temperature while stirring; and the reaction mixture was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated and dried under reduced pressure to yield the title compound as crystals (14 g, 0.068 mol, 58%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.89 (6H, d, J=7.9 Hz), 1.36 (2H, q, J=7.9 Hz), 1.55-1.69 (1H, m), 3.05 (2H, q, J=7.9 Hz), 7.03-7.09 (2H, m), 7.14-7.19 (1H, m), 7.31-7.38 (2H,

m), 7.68 (1H, t, J=4.8 Hz).

[0393]

Example 94

N1-(3-Methylbutyl)-5-(2-((4-hydroxypiperidino)carbonyl)
 5 amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0394]

N,N-dimethylformamide (2.5 ml) and
 4-hydroxypiperidine (213 mg, 2.11 mmol) were added to a
 mixture (243 mg) of phenyl
 10 N-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy
 -2-pyridyl)-carbamate and phenyl
 N-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy
 -2-pyridyl)-N-(phenoxycarbonyl)carbamate synthesized in
 Example 93; and the reaction mixture was stirred for 2 hours.
 15 The reaction mixture was partitioned between ethyl acetate
 and water; the organic layer was concentrated; and the
 residue was purified by NH-silica gel column chromatography
 (ethyl acetate:methanol = 10:1) to yield the title compound
 as white crystals (150 mg, 0.322 mmol).

20 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.91 (6H, d, J=7.2 Hz),
 1.18-1.30 (2H, m), 1.46 (2H, q, J=7.2 Hz), 1.60-1.70 (3H,
 m), 2.97 (2H, m), 3.25-3.35 (2H, m), 3.55-3.64 (1H, m),
 3.69-3.80 (2H, m), 4.63 (1H, d, J=3.4 Hz), 6.53 (1H, dd,
 J=2.3, 5.8 Hz), 6.66 (1H, d, J=3.5 Hz), 7.02 (1H, dd, J=2.3,
 25 8.6 Hz), 7.31 (1H, d, J=2.3 Hz), 7.35 (1H, d, J=2.3 Hz), 7.90
 (1H, d, J=3.5 Hz), 8.06 (1H, d, J=5.8 Hz), 8.16 (1H, t, J=5.8

Hz), 8.26 (1H, t, J=8.6 Hz), 9.08 (1H, s).

[0395]

Example 95

N4-(4-(1-((3-Methylbutyl)amino)carbonyl-1H-5-indolyl)oxy
5 y-2-pyridyl)-4-morpholinecarboxamide

[0396]

N,N-dimethylformamide (5 ml) and morpholine (0.163 ml, 1.87 mmol) were added to a mixture (0.6 g) of phenyl N-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy
10 -2-pyridyl)carbamate and phenyl N-(4-(1-((3-methylbutyl)amino)carbonyl-1H-5-indolyl)oxy
-2-pyridyl)-N-(phenoxycarbonyl)carbamate synthesized in
Example 93; and the reaction mixture was stirred for 2 hours.
The reaction mixture was partitioned between ethyl acetate
15 and water; the organic layer was concentrated; and the
residue was purified by silica gel column chromatography
(Fuji Silysia NH, ethyl acetate: methanol = 10: 1) to yield
the title compound as white crystals (0.202 g, 0.447 mmol).
¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.92 (6H, dd, J=1.7, 7.3
20 Hz), 1.47 (2H, q, J=7.3 Hz), 1.58-1.70 (1H, m), 3.25-3.60
(10H, m), 6.55-6.59 (1H, m), 6.65-6.70 (1H, m), 7.00-7.07
(1H, m), 7.32 (1H, s), 7.37 (1H, m), 7.90 (1H, m), 8.07 (1H,
m), 8.17 (1H, t, J=5.2 Hz), 8.27 (1H, d, J=8.3 Hz), 9.18
(1H, s).

25 [0397]

Example 96

N1-(1-Ethylpropyl)-5-(2-(((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0398]

5 Tetrahydrofuran (20 ml) and triethylamine (1.73 ml, 12.4 mmol) were added to N1-(1-ethylpropyl)-5-(2-amino-4-pyridyl)oxy-1H-1-indole carboxamide (1.45 g, 4.29 mmol); phenyl chloroformate (1.15 ml, 9.1 mmol) was added thereto at 0 °C while stirring; and
10 the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated and subjected to silica gel column chromatography to yield a mixture (1.8 g) of phenyl
15 N-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)-oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate. A portion of 0.6 g of the mixture was dissolved in N,N-dimethylformamide
20 (5 ml); 4-tetrahydro-1H-1-pyrrolylpiperidine (0.7 g, 4.7 mmol) and stirred for 2 hours; the reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; and the residue was purified by silica gel column chromatography (Fuji Silysia NH, ethyl
25 acetate: methanol = 10: 1) to yield as white crystals (202 mg, 0.391 mmol).

MS Spectrum (ESI): 519(M+1).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.90 (6H, t, J=7.5 Hz),
1.20-1.30 (3H, m), 1.47-1.80 (9H, m), 2.03-2.12 (1H, m),
2.40-2.47 (4H, m), 2.77-2.86 (2H, m), 3.62-3.72 (1H, m),
3.88-3.95 (2H, m), 6.53 (1H, dd, J=2.4, 5.9 Hz), 6.66 (1H,
d, J=3.5 Hz), 7.02 (1H, dd, J=2.4, 8.8 Hz), 7.11 (1H, d,
J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.78 (1H, d, J=8.8 Hz),
7.99 (1H, d, J=3.5 Hz), 8.06 (1H, d, J=5.9 Hz), 8.25 (1H,
t, J=8.8 Hz), 9.08 (1H, s).

[0399]

The starting materials were synthesized by following methods.

Production example 96-1

N1-(1-Ethylpropyl)-5-(2-amino-4-pyridyl)oxy-1H-1-indole
carboxamide

[0400]

4-(1H-5-Indolyloxy)-2-pyridinamine (1.85 g, 8.2 mmol,
CAS No. 417722-11-3) which was described in WO 02/32872 was
dissolved in N,N-dimethylformamide (20 ml); and sodium
hydride (394 mg, 9.84 mmol) was added thereto while stirring
at room temperature. The reaction mixture was cooled with
ice bath after 30 minutes; phenyl
N-(1-ethylpropyl)carbamate (1.87 g, 9.03 mmol); and the
reaction mixture was stirred at room temperature for 3 hours.
The reaction mixture was partitioned between ethyl acetate
and water; the organic layer was washed with water and brine,

dried over anhydrous sodium sulfate, concentrated; and the residue was purified by silica gel column chromatography (Fuji Silysia NH, hexane: ethyl acetate = 3: 1) to yield the title compound as crystals (1.95 g, 5.8 mmol, 71%).

5 ^1H -NMR Spectrum (DMSO-d_6) δ (ppm): 0.89 (6H, t, $J=7.5$ Hz), 1.44-1.63 (4H, m), 3.60-3.72 (1H, m), 5.73 (1H, d, $J=2.6$ Hz), 5.80 (2H, s), 6.12 (1H, dd, $J=2.6, 6.0$ Hz), 6.67 (1H, d, $J=4.3$ Hz), 7.00 (1H, dd, $J=2.6, 8.6$ Hz), 7.32 (1H, d, $J=2.6$ Hz), 7.75 (1H, d, $J=6.0$ Hz), 7.98 (1H, d, $J=4.3$ Hz),
10 8.23 (1H, d, $J=8.6$ Hz), 9.30 (1H, s).

[0401]

Production example 96-2

Phenyl N-(1-ethylpropyl)carbamate

[0402]

15 1-Ethylpropylamine (11.6 ml, 100 mmol) was dissolved in tetrahydrofuran (400 ml); pyridine (8.9 ml, 110 mmol) was added thereto at room temperature; and the reaction mixture was stirred. The reaction mixture was cooled with ice bath; phenyl chloroformate (13.8 ml, 110 mmol) was added
20 dropwise; and the reaction mixture was stirred at room temperature for 24 hours. Water was added to the reaction mixture; the reaction mixture was partitioned between ethyl acetate and water; and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent
25 was distilled off under reduced pressure. The obtained crystals were washed with diethyl ether: hexane = 1: 5 to

yield the title compound as crystals (22.3 g, 147 mmol, 59.1%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.87 (6H, t, J=7.5 Hz), 1.30-1.56 (4H, m), 3.20-3.34 (1H, m), 7.03-7.08 (2H, m), 7.14-7.19 (1H, m), 7.32-7.38 (2H, m), 7.51 (1H, d, J=8.7 Hz).

[0403]

Example 97

N1-(1-Ethylpropyl)-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0404]

N,N-Dimethylformamide (4ml) and 4-hydroxypiperidine (360 mg, 3.56 mmol) were added to a mixture (456 mg) of phenyl N-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-carbamate and phenyl N-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate synthesized in Example 96; and the reaction mixture was stirred for 2 hours. The reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; and the residue was purified by silica gel column chromatography (Fuji Silysia NH, ethyl acetate: methanol = 10: 1) to yield the title compound as white crystals (1.37 mg, 0.294 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.90 (6H, t, J=7.5 Hz), 1.18-1.30 (3H, m), 1.45-1.70 (6H, m), 2.92-3.02 (2H, m), 3.55-3.80 (3H, m), 4.63 (1H, d, J=5.1 Hz), 6.53 (1H, m),

6.66 (1H, d, J=3.5 Hz), 7.02 (1H, dd, J=2.5, 8.8 Hz), 7.31 (1H, d, J=2.5 Hz), 7.36 (1H, d, J=2.5 Hz), 7.78 (1H, d, J=8.8 Hz), 7.98 (1H, d, J=3.5 Hz), 8.06 (1H, d, J=5.7 Hz), 8.24 (1H, t, J=8.8 Hz), 9.08 (1H, s).

5 [0405]

Example 98

N4-(4-(1-((1-Ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide

[0406]

10 N,N-dimethylformamide (3ml) and morpholine (0.22 ml, 2.5 mmol) were added to a mixture (0.324 g) of phenyl N-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate and phenyl N-(4-(1-((1-ethylpropyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-N-(phenoxycarbonyl)carbamate synthesized in
15 Example 96; and the reaction mixture was stirred for 2 hours. The reaction mixture was partitioned between ethyl acetate and water; the organic layer was concentrated; and the residue was purified by silica gel column chromatography
20 (Fuji Silysia NH, ethyl acetate: methanol = 10: 1) to yield the title compound as white crystals (95 mg, 0.21 mmol).
¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.91 (6H, t, J=7.5 Hz), 1.45-1.65 (4H, m), 3.37-3.40 (4H, m), 3.48-3.58 (4H, m), 3.62-3.72 (1H, m), 6.56 (1H, dd, J=2.6, 5.8 Hz), 6.68 (1H, d, J=3.5 Hz), 7.02 (1H, dd, J=2.6, 8.8 Hz), 7.31 (1H, d, J=2.6 Hz), 7.36 (1H, d, J=2.6 Hz), 7.80 (1H, d, J= 9.1 Hz),
25

8.00 (1H, d, J=3.5 Hz), 8.08 (1H, d, J=5.8 Hz), 8.26 (1H, d, J=8.8 Hz), 9.18 (1H, s).

[0407]

Example 99

5 N4-(4-(1-((1-Pentyl)amino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide

[0408]

Similarly to Example 90, the title compound was obtained as colorless crystals (131 mg, 0.29 mmol, 84%) from
10 phenyl

N-(4-(1-(1-pentylamino)carbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (200 mg, 0.35 mmol) and morpholine (0.15 ml, 1.7 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.88 (3H, t, J=6.0 Hz),
15 1.31 (4H, m), 1.56 (2H, m), 3.26 (2H, m), 3.35 (4H, m), 3.51 (4H, m), 6.56 (1H, d, J=5.6 Hz), 6.67 (1H, d, J=3.0 Hz), 7.03 (1H, d, J=8.0 Hz), 7.31 (1H, s), 7.36 (1H, s), 7.91 (1H, d, J=3.0 Hz), 8.08 (1H, d, J=5.6 Hz), 8.20 (1H, t, J=5.6 Hz), 8.26 (1H, d, J=8.0 Hz), 9.18 (1H, s).

20 [0409]

The starting materials were synthesized by following procedures.

Production example 99-1

Phenyl N-(1-pentyl)carbamate

25 [0410]

Similarly to Example 90-1, the title compound was

obtained as pale yellow crystals (20.5 g, 99 mmol, 99%) from 1-pentylamine (11.6 ml, 100 mmol), pyridine (8.9 ml, 110 mmol) and phenyl chloroformate (13.8 ml, 110 mmol).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 0.92 (3H, t, J=6.8 Hz), 1.36 (4H, m), 1.58 (2H, m), 3.26 (2H, q, J=6.8 Hz), 5.00 (1H, brs), 7.13 (2H, d, J=7.6 Hz), 7.19 (1H, t, J=7.6 Hz), 7.35 (2H, t, J=7.6 Hz).

[0411]

Production example 99-2

N1-(1-Pentyl)-5-(2-aminopyridin-4-yloxy)-1H-1-indolecarboxamide

[0412]

4-(1H-5-Indolyloxy)-2-pyridinamine (5.0 g, 22 mmol, CAS No. 417722-11-3) which was described in WO 02/32872 was dissolved in N,N-dimethylformamide (60 ml); sodium hydride (1.06 g, 27 mmol) was added thereto at room temperature; and the reaction mixture was stirred for 30 minutes. Phenyl N-n-pentylcarbamate (5.06 g, 24 mmol) while stirring at room temperature; and the reaction mixture was stirred for 30 minutes. The reaction mixture was partitioned between water and ethyl acetate (insoluble portions were perfectly dissolved by adding a small amount of methanol); and the organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia NH; hexane: ethyl acetate=1:1, ethyl acetate,

ethyl acetate: methanol = 95: 5 in this order). The obtained crystals were suspended in hexane: ethanol = 10: 1, filtered off, washed with hexane, and dried under aeration to yield the title compound as colorless crystals (1.55 g, 4.58 mmol, 21%).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.87 (3H, t, J=6.6 Hz), 1.31 (4H m), 1.56 (2H, m), 3.25 (2H, m), 5.74 (1H, d, J=2.8 Hz), 5.83 (2H, s), 6.12 (1H, dd, J=2.8, 5.8 Hz), 6.65 (1H, d, J=3.6 Hz), 7.00 (1H, dd, J=2.0, 8.8 Hz), 7.32 (1H, d, J=2.0 Hz), 7.75 (1H, d, J=5.8 Hz), 7.89 (1H, d, J=3.6 Hz), 8.17 (1H, t, J=5.4 Hz), 8.25 (1H, d, J=8.8 Hz).

[0413]

Production example 99-3

Phenyl

N-(4-((1-pentyl)aminocarbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate

[0414]

Similarly to Example 90-3, the title compound was obtained as a colorless amorphous solid (2.39 g, 4.13 mmol, 90.1%) from N1-(1-pentyl)-5-(2-aminopyridin-4-yloxy)-1H-1-indolecarboxamide (1.55 g, 4.58 mmol), triethylamine (1.43 ml, 10.31 mmol), pyridine (0.56 ml, 6.88 mmol), and phenyl chloroformate (1.44 ml, 11.45 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.87 (3H, t, J=6.4 Hz), 1.31 (4H, m), 1.56 (2H, m), 3.27 (2H, m), 6.56 (1H, d, J=3.6

Hz), 6.96 (1H, dd, J=2.4, 5.4 Hz), 7.09 (1H, dd, J=2.4, 9.0 Hz), 7.16 (4H, d, J=7.6 Hz), 7.29 (2H, t, J=7.6 Hz), 7.43 (5H, m), 7.51 (1H, d, J=2.4 Hz), 7.93 (1H, d, J=2.4 Hz), 8.21 (1H, t, J=5.6 Hz), 8.31 (1H, d, J=9.0 Hz), 8.42 (1H, d, J=5.4 Hz).

[0415]

Example 100

N1-(1-Pentyl)-5-(2-(((4-hydroxypiperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0416]

Similarly to Example 90, the title compound was obtained as colorless crystals (149 mg, 0.320 mmol, 92.6%) from phenyl N-(4-(1-(1-pentyl)aminocarbonyl-1H-indol-5-yloxy)-2-pyridyl)-N-(phenoxycarbonyl)carbamate (200 mg, 0.346 mmol, Production example 99-3) and 4-hydroxypiperidine (174 mg, 1.73 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.87 (3H, m), 1.15-1.40 (6H, m), 1.50-1.70 (4H, m), 2.98 (2H, m), 3.36 (2H, m), 3.59 (1H, m), 3.74 (2H, m), 4.64 (1H, d, J=4.0 Hz), 6.53 (1H, d, J=5.2 Hz), 6.70 (1H, d, J=3.6 Hz), 7.03 (1H, d, J=8.6 Hz), 7.31 (1H, s), 7.35 (1H, s), 7.91 (1H, d, J=3.6 Hz), 8.06 (1H, d, J=5.2 Hz), 8.19 (1H, m), 8.26 (1H, d, J=8.6 Hz), 9.09 (1H, s).

[0417]

Example 101

N1-(1-Pentyl)-5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)amino)pyridin-4-yloxy)-1H-1-indolecarboxamide

[0418]

Similarly to Example 90, the title compound was
 5 obtained as colorless crystals (124 mg, 0.239 mmol, 69.2%)
 from phenyl
 N-(4-(1-(1-pentyl)aminocarbonyl-1H-indol-5-yloxy)-2-pyr
 idyl)-N-(phenoxy carbonyl) carbamate (200 mg, 0.346 mmol,
 Production example 99-3) and 4-(1-pyrrolidinyl)piperidine
 10 (267 mg, 1.73 mmol).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.87 (3H, t, J=6.8 Hz),
 1.20-1.35 (6H, m), 1.52-1.67 (6H, m), 1.74 (2H, m), 2.08
 (1H, m), 2.43 (2H, m), 2.81 (2H, t, J=7.6 Hz), 3.23-3.29
 (4H, m), 3.92 (2H, m), 6.53 (1H, dd, J=2.4, 5.6 Hz), 6.67
 15 (1H, d, J=3.8 Hz), 7.03 (1H, dd, J=2.4, 9.2 Hz), 7.31 (1H,
 d, J=2.4 Hz), 7.35 (1H, d, J=2.4 Hz), 7.91 (1H, t, J=3.8
 Hz), 8.06 (1H, d, J=5.6 Hz), 8.19 (1H, d, J=5.4 Hz), 8.26
 (1H, d, J=9.2 Hz), 9.09 (1H, s).

[0419]

20 Example 102

N1-Methyl-3-chloro-5-(2-(((3-(diethylamino)propyl)amino
)carbonyl)amino-4-pyridyl)oxy)-1H-1-indolecarboxamide

[0420]

Phenyl

25 N-(4-(3-chloro-1-(methylamino)carbonyl-1H-5-indolyl)oxy
 -2-pyridyl) carbamate (160 mg),

3-(diethylamino)propylamine (120 mg),
N,N-dimethylformamide (5ml) were mixed together and stirred
at room temperature for 10 minutes. After the addition of
aqueous sodium hydrogencarbonate, extraction was performed
5 with ethyl acetate. The purification by silica gel column
chromatography (Fuji Silysia NH, ethyl acetate and
sequentially ethyl acetate: methanol = 10: 1) to yield the
title compound as a white solid (86 mg).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.90 (6H, t, J= 7.2 Hz),
10 1.46-1.56 (2H, m), 2.32-2.46 (6H, m), 2.83 (3H, d, J=4.4
Hz), 3.08-3.15 (2H, m), 6.52 (1H, dd, J=5.6, 2.4 Hz), 6.84
(1H, d, J=2.4 Hz), 7.16 (1H, dd, J=8.8, 2.4 Hz), 7.28 (1H,
d, J=2.4 Hz), 8.02 (1H, d, J= 5.6 Hz), 8.09 (2H, s), 8.21
(1H, q, J=4.4 Hz), 8.33 (1H, d, J=8.8 Hz), 9.04 (1H, s).

15 [0421]

The starting materials were synthesized as follows.

Production example 102-1

N1-Methyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-indolecarboxamide

20 [0422]

5-((2-amino-4-pyridyl)oxy)-3-chloro-1H-1-indole
(4.0 g, 15 mmol, CAS No. 417721-98-3) which was described
in WO 02/32872 was dissolved in N,N-dimethylformamide (20
ml); sodium hydride (0.68 g, 60% in oil) and phenyl
25 N-methylcarbamate (2.6 g, the product of Production example
2-1) were added thereto; and the reaction mixture was stirred

at room temperature for 1 hour. The reaction mixture was partitioned between ethyl acetate and water; and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia NH, hexane: ethyl acetate = 1: 2) to yield the title compound as a colorless amorphous solid(1.5 g).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.83 (3H, d, J=4.0 Hz), 5.78 (1H, d, J=2.0 Hz), 5.88 (2H, brs), 6.14 (1H, dd, J=2.0, 5.8 Hz), 7.14 (1H, dd, J=2.4, 9.0 Hz), 7.23 (1H, d, J=2.4 Hz), 7.78 (1H, d, J=5.8 Hz), 8.08 (1H, s), 8.19 (1H, m), 8.32 (1H, d, J=9.0 Hz).

[0423]

Production example 102-2

Phenyl

N-(4-(3-chloro-1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)carbamate

[0424]

While a mixture of N1-methyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indole carboxamide (850 mg, Production example 102-1), triethylamine (0.37 ml), pyridine (320 mg) and N,N-dimethylformamide (10 ml) was cooled with ice and sodium chloride, phenyl chloroformate (630 mg) was added dropwise to the mixture. Aqueous solution of sodium hydrogencarbonate was added thereto after stirring for 20 minutes; extraction was performed with ethyl acetate; and

purification was performed by silica gel column chromatography (ethyl acetate). The crystals precipitated by adding ethyl acetate to the residue were filtered off to yield the title compound as white crystals (160 mg).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.80 (3H, d, J=4.4 Hz), 6.70 (1H, dd, J=5.6, 2.4 Hz), 7.10-7.25 (4H, m), 7.26-7.40 (4H, m), 8.07 (1H, s), 8.18 (2H, m), 8.31 (1H, d, J=8.8 Hz), 10.77 (1H, s).

[0425]

Example 103

N1-Methyl-3-chloro-5-(2-((4-tetrahydro-1H-1-pyrrolyl)piperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0426]

A mixture of N1-methyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indole carboxamide (278 mg, Production example 102-1), triethylamine (0.37 ml), tetrahydrofuran (5 ml) was ice-cooled and stirred; phenyl chloroformate (0.33 ml) was added dropwise to the mixture; and the reaction mixture was further stirred for 10 minutes. Water was added thereto; extraction was performed with ethyl acetate; and purification by silica gel column chromatography was performed to yield a 373 mg of residue. A portion of 245 mg of the residue was dissolved in N,N-dimethylformamide (2 ml); 4-(1-pyrrolidinyl)piperidine (345 mg) was added

thereto; and the reaction mixture was stirred at room temperature for 30 minutes. Extraction was performed with ethyl acetate after the addition of water; and the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia NH) to yield the title compound (154 mg). ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.19-1.30 (2H, m), 1.58-1.68 (4H, m), 1.70-1.78 (2H, m), 2.03-2.13 (1H, m), 2.36-2.46 (4H, m), 2.77-2.87 (5H, m), 3.88-3.97 (2H, m), 6.55 (1H, d, J=5.6 Hz), 7.16 (1H, dd, J=9.2, 2.4 Hz), 7.27^c (1H, d, J=2.4 Hz), 7.32 (1H, s), 8.08 (1H, d, J=5.6 Hz), 8.10 (1H, s), 8.19-8.22 (1H, m), 8.33 (1H, d, J=9.2 Hz), 9.13 (1H, brs).

[0427]

Example 104

N1-Methyl-3-chloro-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0428]

A mixture of N1-methyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indole carboxamide (480 mg, Production example 102-1), triethylamine (0.63 ml), tetrahydrofuran (15 ml) was ice-cooled and stirred; phenyl chloroformate (710 mg) was added dropwise to the mixture; and the reaction mixture was further stirred for 10 minutes. Extraction was performed

with ethyl acetate after addition of water; and purification was performed by silica gel column chromatography (hexane: ethyl acetate = 1: 1). The obtained residue was dissolved in N,N-dimethylformamide (5 ml); 4-hydroxypiperidine (450 mg) was added thereto; and the reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture; extraction was performed with ethyl acetate; and purification was performed by silica gel column chromatography (Fuji Silysia NH, ethyl acetate: methanol = 40: 1) to yield the title compound as colorless powder (78 mg).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.20-1.30 (2H, m), 1.61-1.79 (2H, m), 2.82 (3H, d, J=4.4 Hz), 2.94-3.03 (2H, m), 3.56-3.63 (1H, m), 3.70-3.78 (2H, m), 4.64 (1H, d, J=4.0 Hz), 6.55 (1H, dd, J= 5.6, 2.4 Hz), 7.16 (1H, dd, J= 8.8, 2.4 Hz), 7.27 (1H, d, J=2.4 Hz), 7.32 (1H, d, J=2.4 Hz), 8.08 (1H, d, J= 5.6 Hz), 8.09 (1H, s), 8.21 (1H, q, J=4.4 Hz), 8.32 (1H, d, J=8.8 Hz), 9.13 (1H, s).

[0429]

Example 105

N1-Methyl-3-chloro-5-(2-(((3-(4-hydroxypiperidino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0430]

Similarly to Example 103, the title compound was obtained as white crystals from

1-(3-aminopropyl)-4-hydroxypiperidine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.25-1.38 (2H, m),
1.48-1.58 (2H, m), 1.62-1.70 (2H, m), 1.86-1.97 (2H, m),
2.18-2.25 (2H, m), 2.60-2.68 (2H, m), 2.83 (3H, d, J=3.6
5 Hz), 3.02-3.13 (2H, m), 3.34-3.42 (1H, m), 4.49 (1H, d, J=4.0
Hz), 6.52 (1H, dd, J=6.0, 2.4 Hz), 6.84-6.86 (1H, m), 7.17
(1H, dd, J=8.8, 2.4 Hz), 7.28 (1H, d, J=2.4 Hz), 8.01-8.05
(2H, m), 8.10 (1H, s), 8.19-8.24 (1H, m), 8.33 (1H, d, J=8.8
Hz), 9.04 (1H, brs).

10 [0431]

The starting materials were synthesized as follows.

Production example 105-1

2-(3-(4-Hydroxypiperidino)propyl)isoindolin-1,3-dione

[0432]

15 N-(3-bromopropyl)phthalimide (26.8 g),
4-hydroxypiperidine (15.0 g) and potassium carbonate (27.6
g) were added to N,N-dimethylformamide; and the reaction
mixture was stirred at room temperature overnight. After
the addition of water, extraction was performed with ethyl
20 acetate; the organic layer was washed with water and brine,
dried over anhydrous sodium sulfate, and concentrated under
reduced pressure to yield the title compound (13.9 g).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.40-2.05 (6H, m), 2.10-2.60
(4H, m), 2.70-2.90 (2H, m), 3.60-3.85 (3H, m), 7.70-7.75
25 (2H, m), 7.82-7.87 (2H, m).

[0433]

Production example 105-2Benzyl N-(3-(4-hydroxypiperidino)propyl)carbamate

[0434]

Ethanol (100 ml) and hydrazine hydrate (1.5 g) were
5 added to
2-(3-(4-hydroxypiperidino)propyl)isoindolin-1,3-dione
(4.5 g); the reaction mixture was heated to reflux for 2.5
hours; and the produced crystals were filtered off.
N-Methylmorpholine (2.5 ml) and
10 N-(benzyloxycarbonyloxy)succinimide (5.2 g) were added to
the filtrate; and the reaction mixture was stirred at room
temperature overnight. Aqueous solution of sodium
hydrogencarbonate was added to the reaction mixture;
extraction was performed with ethyl acetate; and the organic
15 layer was washed with water and brine, dried over anhydrous
sodium sulfate, and concentrated under reduced pressure.
The residue was purified by silica gel column chromatography
to yield the title compound (2.96 g).

¹H-NMR Spectrum (CDCl₃) δ (ppm): 1.52-2.10 (6H, m), 2.10-2.60
20 (4H, m), 2.78-2.90 (2H, m), 3.24-3.33 (2H, m), 3.53-3.86
(1H, m), 5.09 (2H, s), 5.88-5.96 (1H, m), 7.28-7.38 (5H,
m).

[0435]

Production example 105-31-(3-Aminopropyl)-4-hydroxypiperidine

[0436]

Ethanol (200 ml) and palladium carbon (2.5 g) were added to benzyl N-(3-(4-hydroxypiperidino)propyl)carbamate (2.96 g); and the reaction mixture was stirred vigorously under hydrogen atmosphere overnight. Palladium carbon was removed by filtration, and the filtrate was concentrated to yield the title compound (1.5 g).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.25-1.38 (2H, m), 1.41-1.49 (2H, m), 1.61-1.69 (2H, m), 1.84-1.95 (2H, m), 2.18-2.25 (2H, m), 2.49-2.57 (2H, m), 2.58-2.69 (2H, m), 3.30-3.42 (1H, m).

[0437]

Example 106

N1-Methyl-3-chloro-5-(2-((4-(2-hydroxyethyl)piperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0438]

Similarly to Example 104, the title compound was obtained from 4-(2-hydroxyethyl)piperazine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.30-2.48 (6H, m), 2.82 (3H, d, J=4.4 Hz), 3.30-3.40 (4H, m), 3.46 (2H, q, J=5.6 Hz), 4.38 (1H, t, J=5.6 Hz), 6.57 (1H, dd, J=5.6, 2.4 Hz), 7.16 (1H, dd, J=8.8, 2.4 Hz), 7.29 (1H, d, J=2.4 Hz), 7.32 (1H, d, J=2.4 Hz), 8.07-8.13 (2H, m), 8.21 (1H, q, J=4.4 Hz), 8.32 (1H, d, J=8.8 Hz), 9.15 (1H, s).

[0439]

Example 107

N4-(4-(3-Chloro-1-(methylamino)carbonyl-1H-5-indolyl)oxy-2-pyridyl)-4-morpholinecarboxamide

[0440]

Similarly to Example 104, the title compound was
5 obtained from morpholine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.82 (3H, d, J=4.4 Hz),
3.33-3.40 (4H, m), 3.49-3.56 (4H, m), 6.58 (1H, dd, J=5.6,
2.4 Hz), 7.16 (1H, dd, J=8.8, 2.4 Hz), 7.27 (1H, d, J= 2.4
Hz), 7.32 (1H, d, J=2.4 Hz), 8.06-8.13 (2H, m), 8.21 (1H,
10 q, J=4.4 Hz), 8.32 (1H, d, J=8.8 Hz), 9.22 (1H, s).

[0441]

Example 108

N1-Methyl-3-chloro-5-(2-((4-ethylpiperazino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

15 [0442]

Similarly to Example 103, the title compound was
obtained from N-ethylpiperazine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.96 (3H, t, J=7.2 Hz),
2.24-2.32 (6H, m), 2.82 (3H, d, J=4.0 Hz), 3.34-3.39 (4H,
20 m), 6.57 (1H, dd, J=6.0, 2.4 Hz), 7.17 (1H, dd, J=9.2, 2.4
Hz), 7.27 (1H, d, J=2.4 Hz), 7.32 (1H, d, J=2.4 Hz), 8.07-8.10
(2H, m), 8.18-8.25 (1H, m), 8.33 (1H, d, J=9.2 Hz), 9.17
(1H, brs).

[0443]

25 Example 109

N1-Ethyl-3-chloro-5-(2-((4-hydroxypiperidino)carbonyl)a

mino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0444]

Similarly to Example 104, the title compound was obtained as a colorless amorphous solid from

5 N1-ethyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indolecarboxamide.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.15 (2H, m), 1.61 (3H, t, J=7.2 Hz), 1.60-1.70 (2H, m), 2.94-3.02 (2H, m), 3.26-3.36 (2H, m), 3.56-3.63 (1H, m), 3.70-3.78 (2H, m), 4.64 (1H, d, J= 4.4 Hz), 6.55 (1H, dd, J=5.6, 2.4 Hz), 7.16 (1H, dd, J= 8.8, 2.4 Hz), 7.27 (1H, d, J=2.4 Hz), 7.32 (1H, d, J=2.4 Hz), 8.08 (1H, d, J= 5.6 Hz), 8.13 (1H, s), 8.22-8.27 (1H, m), 8.32 (1H, d, J=8.8 Hz), 9.12 (1H, s).

10

[0445]

15 The starting material was synthesized as follows.

Production example 109-1

N1-Ethyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indolecarboxamide

[0446]

20 Phenyl N-ethylcarbamate was added to a solution of 5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indole (1.35 g, CAS No. 417721-98-3) which was described in WO 02/32872, sodium hydride (210 mg) and N,N-dimethylformamide; and the reaction mixture was stirred for 1 hour. An aqueous solution

25 of ammonium chloride was added to the reaction mixture; extraction was performed with ethyl acetate; and

purification by silica gel column chromatography (Fuji Silysia NH, hexane: ethyl acetate = 1: 2) to yield the title compound as a colorless oil (1.07 g).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.15 (3H, t, J=7.2 Hz),
 3.25-3.35 (2H, m), 5.76 (1H, d, J=2.4 Hz), 5.87 (2H, s),
 6.14 (1H, dd, J=5.6, 2.4 Hz), 7.13 (1H, dd, J=8.8, 2.4 Hz),
 7.23 (1H, d, J=2.4 Hz), 7.77 (1H, d, J=5.6 Hz), 8.11 (1H, s),
 8.20-8.25 (1H, m), 8.31 (1H, d, J=8.8 Hz).

[0447]

Example 110

N1-Ethyl-3-chloro-5-(2-(((3-(4-hydroxypiperidino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0448]

Similarly to Example 103, the title compound was obtained as white crystals from N1-ethyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indolecarboxamide and 1-(3-aminopropyl)-4-hydroxypiperidine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.16 (3H, t, J=7.2 Hz),
 1.26-1.38 (2H, m), 1.48-1.57 (2H, m), 1.63-1.70 (2H, m),
 1.86-1.97 (2H, m), 2.18-2.25 (2H, m), 2.60-2.68 (2H, m),
 3.05-3.13 (2H, m), 3.26-3.34 (2H, m), 3.34-3.42 (1H, m),
 4.49 (1H, d, J=4.0 Hz), 6.52 (1H, dd, J=6.0, 2.4 Hz), 6.84-6.86
 (1H, m), 7.16 (1H, dd, J=8.8, 2.4 Hz), 7.28 (1H, d, J=2.4
 Hz), 7.98-8.05 (2H, m), 8.14 (1H, s), 8.22-8.28 (1H, m),
 8.33 (1H, d, J=8.8 Hz), 9.03 (1H, brs).

[0449]

Example 111

N1-Ethyl-3-chloro-5-(2-(((3-(diethylamino)propyl)amino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

5 [0450]

Similarly to Example 104, the title compound was obtained from N1-ethyl-5-(2-amino-4-pyridyl)oxy-3-chloro-1H-1-indolecarboxamide and 3-(diethylamino)propylamine.

10 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.90 (6H, t, J=7.2 Hz), 1.16 (3H, t, J=7.2 Hz), 1.46-1.54 (2H, m), 2.33-2.44 (6H, m), 3.07-3.14 (2H, m), 3.26-3.34 (2H, m), 6.52 (1H, dd, J=5.6, 2.4 Hz), 6.83 (1H, s), 7.16 (1H, dd, J=8.8, 2.4 Hz), 7.28 (1H, d, J=2.4 Hz), 8.02 (1H, d, J=5.6 Hz), 8.04-8.13 (1H, brs), 8.14 (1H, s), 8.23-8.27 (1H, m), 8.33 (1H, d, J=8.8 Hz), 9.04 (1H, s).

[0451]

Example 112

N1,3-Dimethyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

20

[0452]

Similarly to Example 104, the title compound was obtained as a colorless amorphous solid from N1,3-dimethyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide.

25

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17-1.30 (2H, m),

1.61-1.70 (2H, m), 2.19 (3H, s), 2.80 (3H, d, J=4.0 Hz),
2.94-3.03 (2H, m), 3.56-3.64 (1H, m), 3.70-3.78 (2H, m),
4.64 (1H, d, J=4.0 Hz), 6.52 (1H, dd, J=5.6, 2.4 Hz), 7.02
(1H, dd, J=8.8, 2.4 Hz), 7.29-7.33 (2H, m), 7.66 (1H, s),
5 8.00 (1H, q, J=4.0 Hz), 8.05 (1H, d, J=5.6 Hz), 8.25 (1H,
d, J=8.8 Hz), 9.08 (1H, s).

[0453]

The starting materials were synthesized as follows.

Production example 112-1

10 4-(3-Methyl-1H-5-indolyl)oxy-2-pyridinamine

[0454]

A mixture of 5-hydroxy-3-methylindole (4.7 g),
2-amino-4-chloropyridine (4.1 g), sodium hydride (1.3 g),
and dimethyl sulfoxide (40 ml) was stirred at 160 °C for
15 hours. Water was added thereto; extraction was performed
with ethyl acetate; and purification was performed by silica
gel column chromatography (ethyl acetate, sequentially,
ethyl acetate: methanol=20:1). The solvent was distilled
off to yield the title compound as a brown solid (1.6 g).

20 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.29 (3H, s), 5.70 (1H,
d, J=2.4 Hz), 5.77 (2H, s), 6.10 (1H, dd, J=5.6, 2.4 Hz),
6.80 (1H, dd, J=8.8, 2.4 Hz), 7.15 (1H, s), 7.17 (1H, d,
J=2.4 Hz), 7.35 (1H, d, J=8.8 Hz), 7.72 (1H, d, J=5.6 Hz),
10.83 (1H, s).

25 [0455]

Production example 112-2

N1,3-Dimethyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0456]

Phenyl N-methylcarbamate (350 mg, Production example 2-1) was added to a solution of 4-(3-methyl-1H-5-indolyl)oxy-2-pyridinamine (500 mg), sodium hydride (93 mg) and N,N-dimethylformamide (5 ml) at room temperature; and the reaction mixture was stirred for 2 hours and 45 minutes. Water was added to the reaction mixture; extraction was performed with ethyl acetate; and purification was performed by NH-silica gel column chromatography (Fuji Silysia, hexane: ethyl acetate = 1: 2, sequentially, ethyl acetate) to yield the title compound as a pale yellow amorphous solid (365 mg).

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 2.19 (3H, s), 2.80 (3H, d, J=4.0 Hz), 5.73 (1H, d, J=2.4 Hz), 5.83 (2H, s), 6.12 (1H, dd, J=5.6, 2.4 Hz), 7.00 (1H, dd, J=8.8, 2.4 Hz), 7.27 (1H, d, J= 2.4 Hz), 7.64 (1H, s), 7.75 (1H, d, J=5.6 Hz), 7.98 (1H, q, J=4.0 Hz), 8.24 (1H, d, J=8.8 Hz).

[0457]

Example 113

N1,3-Dimethyl-5-(2-((4-tetrahydro-1H-pyrrolyl)piperidino)carbonyl)amino-4-pyridyl)oxy-1H-1-indolecarboxamide

[0458]

Similarly to Example 104, the title compound was obtained as a colorless amorphous solid from

N1,3-dimethyl-5-(2-amino-4-pyridyl)oxy-1H-1-indolecarboxamide and 4-(1-pyrrolidinyl)piperidine.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 1.17-1.79 (2H, m), 1.60-1.67 (4H, m), 1.70-1.79 (2H, m), 2.03-2.13 (1H, m), 2.19 (3H, s), 2.40-2.57 (4H, m), 2.77-2.86 (5H, m), 3.88-3.96 (2H, m), 6.52 (1H, dd, J= 5.6, 2.4 Hz), 7.02 (1H, dd, J=8.8, 2.4 Hz), 7.28-7.85 (2H, m), 7.66 (1H, s), 8.00 (1H, q, J=4.0 Hz), 8.05 (1H, d, J=5.6 Hz), 8.25 (1H, d, J=8.8 Hz), 9.08 (1H, s).

[0459]

Example 114

N1-Cyclopropyl-5-(2-((4-hydroxypiperidino)carbonyl)amino-4-pyridyl)oxy-3-methyl-1H-1-indolecarboxamide

[0460]

Similarly to Example 104, the title compound was obtained as a colorless amorphous solid from N1-cyclopropyl-5-(2-amino-4-pyridyl)oxy-3-methyl-1H-1-indolecarboxamide.

¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.56-0.60 (2H, m), 2.67-2.73 (2H, m), 1.19-1.29 (2H, m), 1.61-1.70 (2H, m), 2.18 (3H, s), 2.72-2.78 (1H, m), 2.94-3.03 (2H, m), 3.56-3.63 (1H, m), 3.70-3.77 (2H, m), 4.64 (1H, d, J=4.0 Hz), 6.51 (1H, dd, J=5.6, 2.4 Hz), 7.02 (1H, dd, J=8.8, 2.4 Hz), 7.28-7.32 (2H, m), 7.65 (1H, s), 8.05 (1H, d, J=5.6 Hz), 8.11 (1H, d, J=2.4 Hz), 8.24 (1H, d, J=8.8 Hz), 9.08 (1H, s).

[0461]

The starting material was synthesized as follows.

Production example 114-1

N1-Cyclopropyl-5-(2-amino-4-pyridyl)oxy-3-methyl-1H-1-i
5 ndolecarboxamide

[0462]

Similarly to Production example 112-2, the title compound was obtained as a colorless amorphous solid from phenyl N-cyclopropylcarbamate.

10 ¹H-NMR Spectrum (DMSO-d₆) δ (ppm): 0.55-0.60 (2H, m),
0.68-0.73 (2H, m), 2.18 (3H, s), 2.70-2.79 (1H, m), 5.73
(1H, d, J=2.4 Hz), 5.83 (2H, s), 6.12 (1H, dd, J=5.6, 2.4
Hz), 7.00 (1H, dd, J=8.8, 2.4 Hz), 7.26 (1H, d, J=2.4 Hz),
7.63 (1H, s), 7.75 (1H, d, J=5.6 Hz), 8.09 (1H, d, J=2.4
15 Hz), 8.23 (1H, d, J=8.8 Hz).

[0463]

Example 115

N1-Cyclopropyl-5-(2-((4-(2-hydroxyethyl)piperazino)carb
onyl)amino-4-pyridyl)oxy-3-methyl-1H-1-indolecarboxamid
20 e

[0464]

Similarly to Example 104, the title compound was obtained as a colorless amorphous solid from N1-cyclopropyl-5-(2-amino-4-pyridyl)oxy-3-methyl-1H-1-i
25 ndolecarboxamide and 1-(2-hydroxyethyl)piperazine.

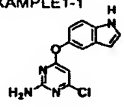
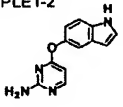
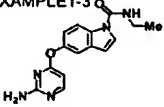

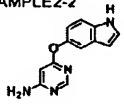
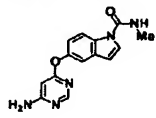
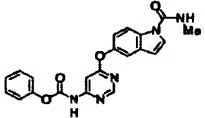
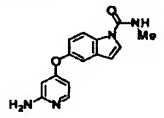
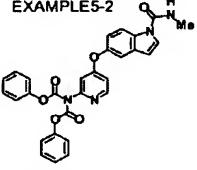
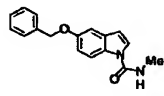
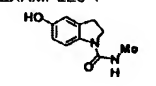
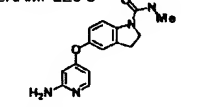
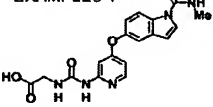
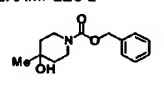
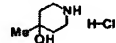
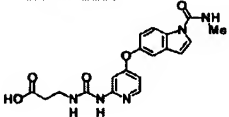
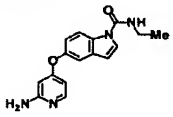
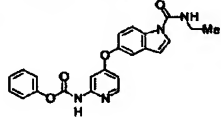
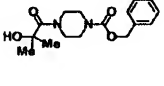
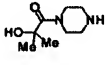
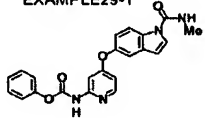
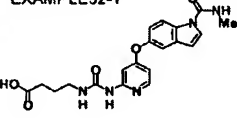
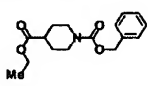
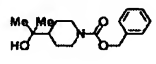
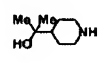
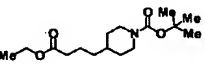
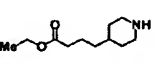
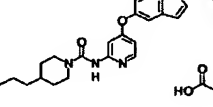
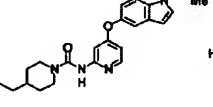
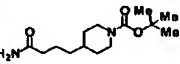
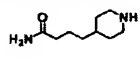
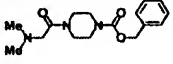
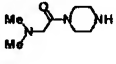
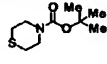
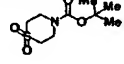

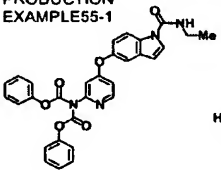
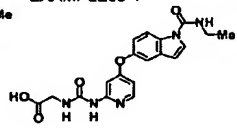
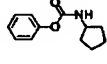
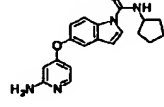
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0.67-0.74 (2H, m), 2.18 (3H, s), 2.30-2.37 (6H, m), 2.70-2.78 (1H, m), 3.30-3.38 (4H, m), 3.46 (2H, q, J=6.4 Hz), 4.38 (1H, t, J=6.4 Hz), 6.53 (1H, dd, J=5.6, 2.4 Hz), 7.02 (1H, dd, J=8.8, 2.4 Hz), 7.28-7.32 (2H, m), 7.65 (1H, s), 8.06 (1H, d, J=5.6 Hz), 8.11 (1H, d, J=2.4 Hz), 8.24 (1H, d, J=8.8 Hz), 9.10 (1H, s).

The structural formulas of the compounds obtained in Production examples and Examples above are shown in Tables 3 to 8 below.

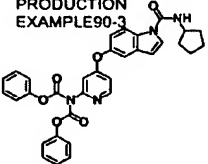
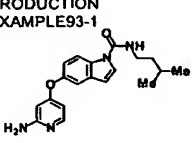
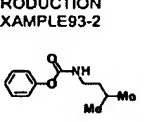
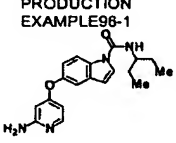
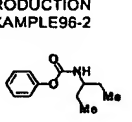
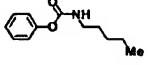
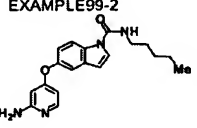
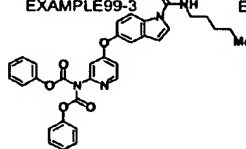
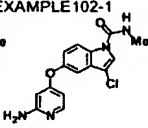
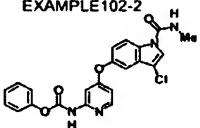
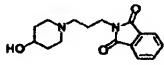
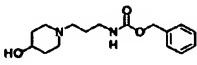
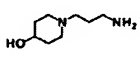
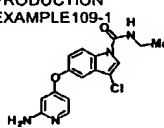
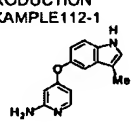
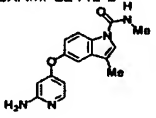
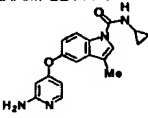
[0465]

[Table 3]

PRODUCTION EXAMPLE1-1 	PRODUCTION EXAMPLE1-2 	PRODUCTION EXAMPLE1-3 	PRODUCTION EXAMPLE2-1 	PRODUCTION EXAMPLE2-2 
PRODUCTION EXAMPLE2-3 	PRODUCTION EXAMPLE2-4 	PRODUCTION EXAMPLE5-1 	PRODUCTION EXAMPLE5-2 	PRODUCTION EXAMPLE5-3 
PRODUCTION EXAMPLE5-4 	PRODUCTION EXAMPLE5-5 	PRODUCTION EXAMPLE8-1 	PRODUCTION EXAMPLE8-2 	PRODUCTION EXAMPLE8-3 
PRODUCTION EXAMPLE26-1 	PRODUCTION EXAMPLE27-1 	PRODUCTION EXAMPLE27-2 	PRODUCTION EXAMPLE28-1 	PRODUCTION EXAMPLE28-2 
PRODUCTION EXAMPLE29-1 	PRODUCTION EXAMPLE32-1 	PRODUCTION EXAMPLE42-1 	PRODUCTION EXAMPLE42-2 	PRODUCTION EXAMPLE42-3 
PRODUCTION EXAMPLE43-1 	PRODUCTION EXAMPLE43-2 	PRODUCTION EXAMPLE43-3 	PRODUCTION EXAMPLE43-4 	PRODUCTION EXAMPLE44-1 
PRODUCTION EXAMPLE44-2 	PRODUCTION EXAMPLE51-1 	PRODUCTION EXAMPLE51-2 	PRODUCTION EXAMPLE54-1 	PRODUCTION EXAMPLE54-2 
PRODUCTION EXAMPLE54-3 	PRODUCTION EXAMPLE55-1 	PRODUCTION EXAMPLE59-1 	PRODUCTION EXAMPLE90-1 	PRODUCTION EXAMPLE90-2 

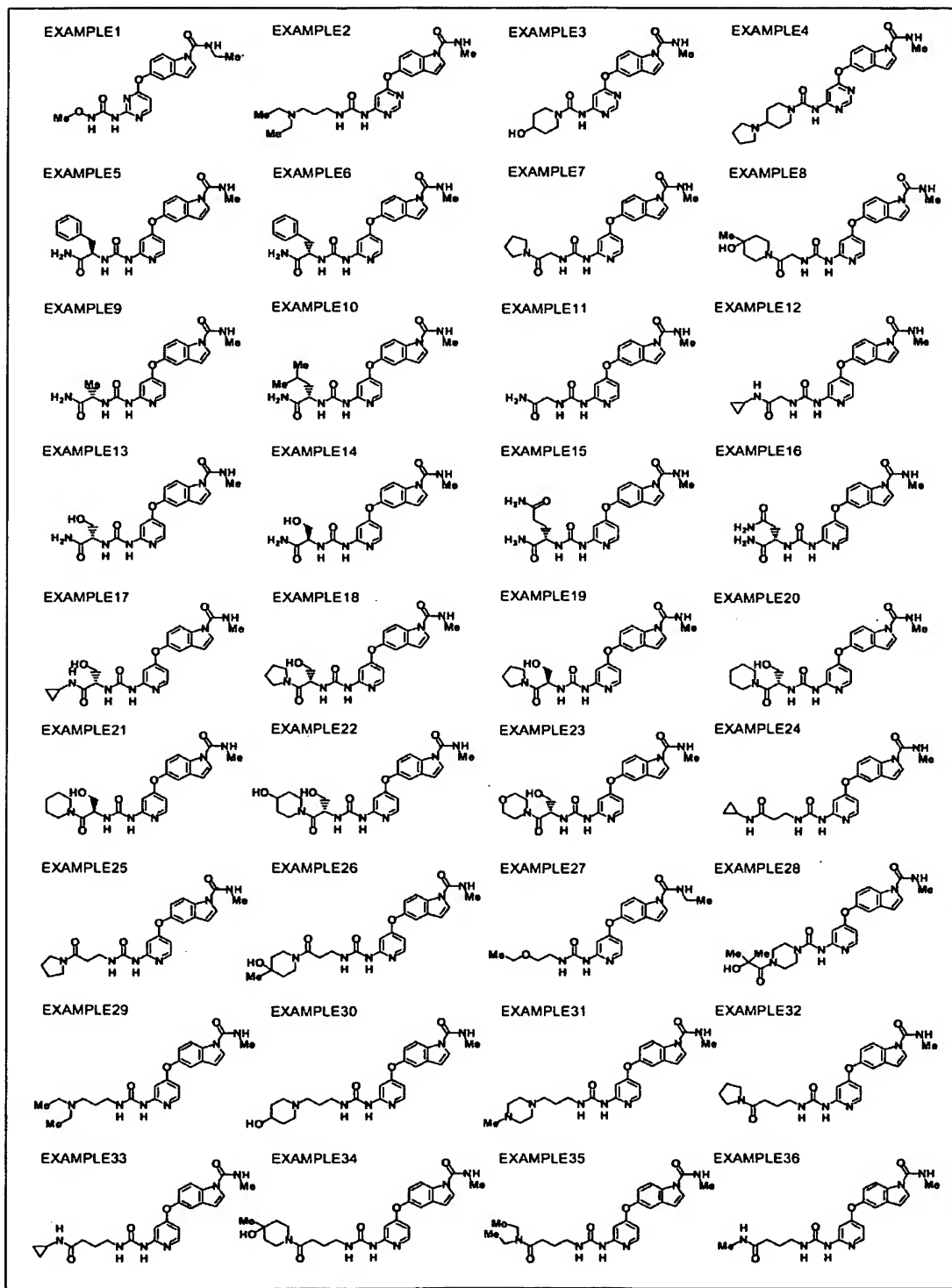
[0466]

[Table 4]

<p>PRODUCTION EXAMPLE90-3</p> 	<p>PRODUCTION EXAMPLE93-1</p> 	<p>PRODUCTION EXAMPLE93-2</p> 	<p>PRODUCTION EXAMPLE96-1</p> 	<p>PRODUCTION EXAMPLE96-2</p> 
<p>PRODUCTION EXAMPLE99-1</p> 	<p>PRODUCTION EXAMPLE99-2</p> 	<p>PRODUCTION EXAMPLE99-3</p> 	<p>PRODUCTION EXAMPLE102-1</p> 	<p>PRODUCTION EXAMPLE102-2</p> 
<p>PRODUCTION EXAMPLE105-1</p> 	<p>PRODUCTION EXAMPLE105-2</p> 	<p>PRODUCTION EXAMPLE105-3</p> 	<p>PRODUCTION EXAMPLE109-1</p> 	<p>PRODUCTION EXAMPLE112-1</p> 
<p>PRODUCTION EXAMPLE112-2</p> 	<p>PRODUCTION EXAMPLE114-1</p> 			

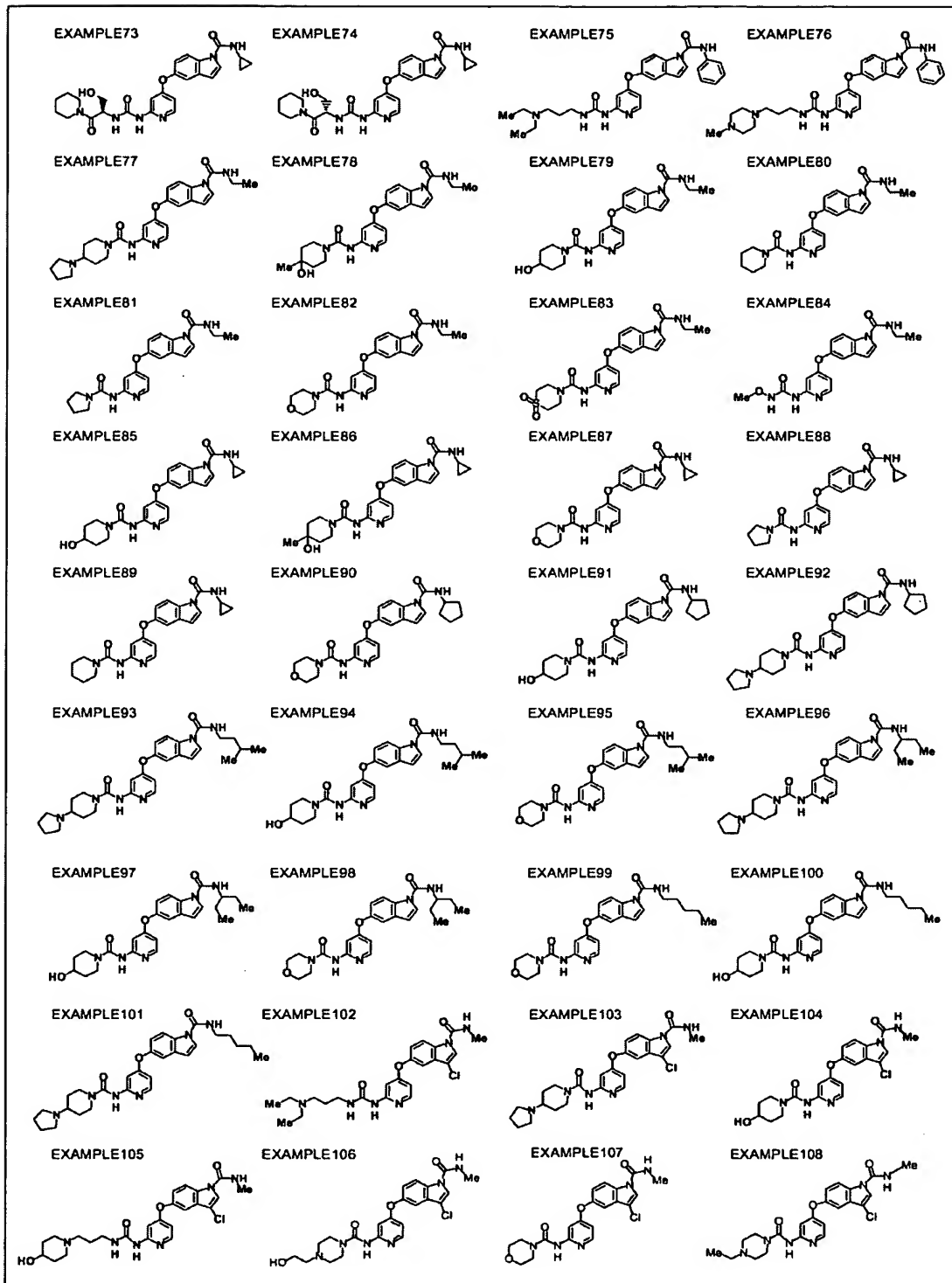
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[Table 5]



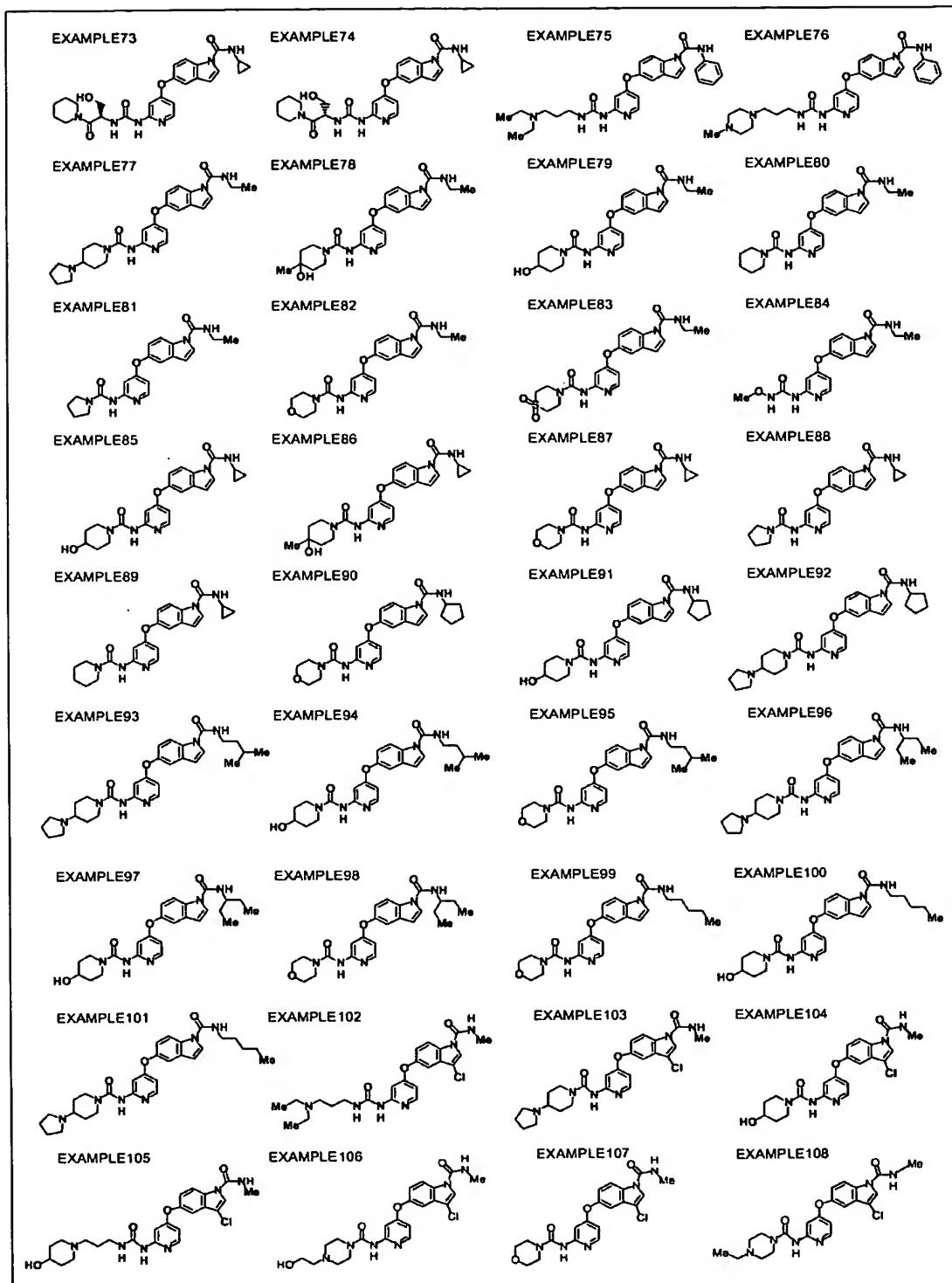
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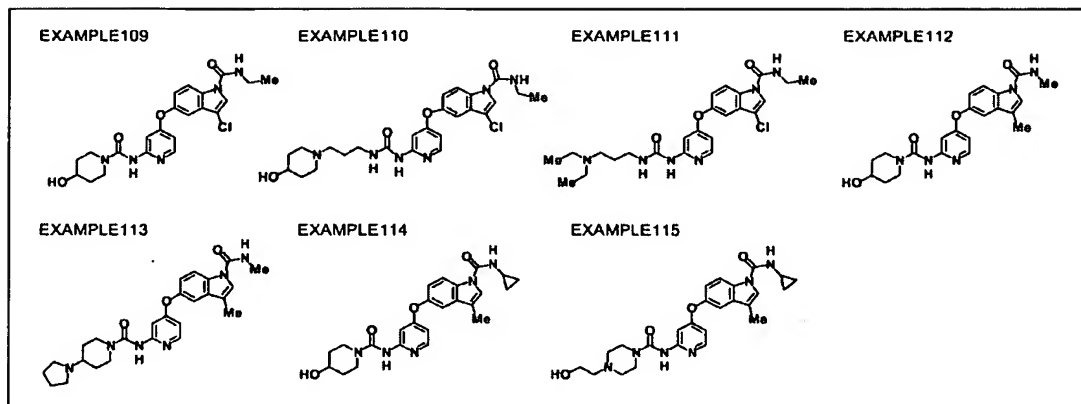
[0469]

[Table 7]



[0470]

[Table 8]



[0471]

[Effects of the invention]

According to the present invention, it is possible to provide novel compounds that exhibit (1) powerful
5 inhibitory action against tube formation by vascular endothelial cells induced by VEGF or FGF and (2) powerful inhibitory action against receptor kinases for VEGF or FGF, and which are highly useful as medicines.

It should be noted that the tube formation of vascular
10 endothelial cells is an important process in angiogenesis, and a compound having inhibitory action therefor has angiogenesis inhibitory action. In addition, it is known that angiogenesis in body progresses by the additive/synergistic effect of a plurality of angiogenic
15 factors represented by VEGF and FGF (Koolwijk P, van Erck MGM, de Vree WJA, Vermeer MA, Weich HA, Hance maaijer R, van Hinsberg VWM, . Cooperative effect of TNF-alpha, bFGF and VEGF on the formation of tubular structures of human microvascular endothelial cells in a fibrin matrix. Role
20 of urokinase activity. J. Cell Biol., 132 P. 1177-1188, (1996)).

Therefore, the compounds of the invention which inhibit tube formation induced by VEGF or FGF produced by cancer cells and the like are expected to exhibit powerful
25 angiogenesis inhibition *in vivo*, and should be highly useful as angiogenesis inhibitors. Moreover, the compounds of the

invention are highly useful as angiogenesis inhibitors, and
 are also useful as prophylactic or therapeutic agents for
 diseases for which angiogenesis inhibition is effective,
 angiogenesis inhibitors, antitumor agents, therapeutic
 5 agents for angioma, cancer metastasis inhibitors,
 therapeutic agents for retinal neovascularization,
 therapeutic agents for diabetic retinopathy, therapeutic
 agents for inflammatory disease, therapeutic agents for
 inflammatory disease selected from deformed arthritis,
 10 rheumatoid arthritis, psoriasis or delayed hypersensitivity
 reaction, therapeutic agents for atherosclerosis, and
 angiogenesis inhibition-based antitumor agents.

[0472]

[Sequence Listing]

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<211> 21

<212> DNA

<213> Artifical Sequence

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21